The National Academies of
SCIENCES • ENGINEERING • MEDICINE

Board on Health Sciences Policy

Roundtable on Genomics and Precision Health

Spring 2017 Meeting

March 9, 2017

Keck Center
Room 100
500 Fifth Street NW
Washington, DC

The National Academies of
SCIENCES • ENGINEERING • MEDICINE

Board on Health Sciences Policy

Roundtable on Genomics and Precision Health

Spring 2017 Meeting of the Genomics Roundtable

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March 9, 2017
Washington, DC

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AGENDA

The National Academies of
SCIENCES • ENGINEERING • MEDICINE

Board on Health Sciences Policy
Roundtable on Genomics and Precision Health

31st Meeting of the Roundtable on Genomics and Precision Health

March 9, 2017

Keck Building of the National Academies
500 Fifth Street NW
Room 100
Washington, DC 20001

8:00 A.M. **Working Breakfast (Keck 100)**

SESSION I: WELCOME

8:15 A.M. **Welcoming Remarks**

Geoffrey Ginsburg, *Roundtable Co-Chair*
Director, Duke Center for Applied Genomics & Precision Medicine; Professor of Medicine and of Pathology and Biomedical Engineering, Duke University Medical Center

8:20 A.M. **Director's Report**

Siobhan Addie
Associate Program Officer
Board on Health Sciences Policy
The National Academies of Sciences, Engineering, and Medicine

SESSION II: ACCELERATING PRECISION HEALTH BY UTILIZING GENOMICS AND GENETICS

Objectives:

- Discuss recent Roundtable activities including the public workshop on genetics-based clinical trials and the Genomics and Population Health action collaborative.
- Learn about new research on access and coverage for genomic medicine

8:30 A.M. **Recap from *Enabling Precision Medicine: The Role of Genetics in Clinical Drug Development – A Workshop***

Laura Nisenbaum, *Workshop Co-Chair*
Advisor, Chorus Clinical Development
Eli Lilly and Company

8:50 A.M. **Discussion with Members**

9:10 A.M. **New Research on Genomic Medicine: Access, Coverage, and Ethics**

Christine Lu
Assistant Professor, Department of Population Medicine
Harvard Medical School

9:25 A.M. **Discussion with Members**

9:45 A.M. **The Genomics and Population Health Action Collaborative: Outcomes from Year 1 and Outlook for Year 2**

Muin Khoury
Director, Office of Public Health Genomics
Centers for Disease Control and Prevention

10:00 A.M. **Discussion with Members**

10:15 A.M. **Break**

SESSION III: EXPLORING THE ISSUES SURROUNDING THE USE OF DATA COLLECTED FROM MOBILE HEALTH APPLICATIONS

Objectives:

- Examine the major challenges that surround the design of mHealth applications and the collection of highly complex data for research and clinical care, including data quality and analytics, privacy/security, data ownership, and patient consent processes.
- Learn how mHealth applications that include genomic and EHR data could fit into the clinical workflow.

Co-Moderators:
Ann Cashion, National Institute for Nursing Research, and Geoffrey Ginsburg, Duke University

10:30 A.M. **Strategies for Delivering Value from Digital Technology**

Eric D. Perakslis
Senior Vice President of Informatics
Takeda

10:50 A.M. **Analyzing the Value of Wearable Biosensors for Collecting Useful Health Information**

Michael P. Snyder
Professor and Chair of Genetics
Stanford University

11:10 A.M. **Discussion with Members**

11:45 A.M. **Working Lunch (Overview Group to meet in Room 103)**

SESSION IV: ASSESSING THE RETURN ON INVESTMENT OF GENOMIC MEDICINE

Objectives:

- Gather information on how return on investment of genomic medicine tests/services is assessed and acted upon.
- Explore the economic considerations that underlie the decision to implement genomic medicine programs, from the perspective of payers, health economists, and integrated health care systems.

Co-Moderators:
Sheri Schully, National Institutes of Health, and Sam Shekar, Northrup Grumman

12:30 P.M. **Perspective 1: Health Care Delivery System Specializing in Pediatrics**

John Barnard
President, The Research Institute
Nationwide Children's Hospital

12:45 P.M. **Perspective 2: Health Care Delivery System**

Murray Brilliant
Director (Marshfield Clinic), Translational Technologies & Resources
University of Wisconsin Institute for Clinical and Translational Research

1:00 P.M. **Perspective 3: Payer**

Jeffrey Hankoff
Medical Officer
Cigna

1:15 P.M. **Perspective 4: Health Economist**

Mark Fendrick
Professor, Department of Internal Medicine
University of Michigan

1:30 P.M. **Panel Discussion**

Reactant:
Scott Grosse *(via WebEx)*
Research Economist
Centers for Disease Control and Prevention (CDC)

2:10 P.M. **Break**

SESSION V: CURRENT ACTIVITIES AND FUTURE PLANNING

Objectives:

- Roundtable Interest Groups meet separately to discuss ongoing projects, priorities, and areas of interest for 2017
- Share information from individual interest groups back with the full Roundtable membership.
- Discuss areas of emphasis and confirm next steps for remaining 2017 meetings and a potential workshop in November 2017.

2:20 P.M. **Interest Group Breakouts**

Goal review and activity planning:

- Discovery/Development to Enable Precision Medicine (Keck 100)
- Implementation and Public Health Systems (Keck 103)
- Intersection of Genomics/Genetics and Precision Health and mHealth (Keck 207)

2:50 P.M. **Report-outs from Interest Group Discussions – Keck 100**

3:10 P.M. **Reflections on the Day and Discussion of Next Steps**

3:35 P.M. **Final Words from Roundtable Co-Chair**

3:45 P.M. **Adjourn**

ROUNDTABLE INFORMATION

The National Academies of
SCIENCES • ENGINEERING • MEDICINE

ROUNDTABLE ON GENOMICS AND PRECISION HEALTH

The sequencing of the human genome is rapidly opening new doors to research and progress in biology, medicine, and health care. At the same time, these developments have produced a diversity of new issues to be addressed.

The National Academies of Sciences, Engineering, and Medicine has convened a Roundtable on Genomics and Precision Health (previously the Roundtable on Translating Genomic-Based Research for Health) that brings together leaders from academia, industry, government, foundations and associations, and representatives of patient and consumer interests who have a mutual concern and interest in addressing the issues surrounding the translation of genome-based research for use in maintaining and improving health. The mission of the Roundtable is to advance the field of genomics and improve the translation of research findings to health care, education, and policy. The Roundtable will discuss the translation process, identify challenges at various points in the process, and discuss approaches to address those challenges.

The field of genomics and its translation involves many disciplines, and takes place within different economic, social, and cultural contexts, necessitating a need for increased communication and understanding across these fields. As a convening mechanism for interested parties from diverse perspectives to meet and discuss complex issues of mutual concern in a neutral setting, the Roundtable: fosters dialogue across sectors and institutions; illuminates issues, but does not necessarily resolve them; and fosters collaboration among stakeholders.

To achieve its objectives, the Roundtable conducts structured discussions, workshops, and symposia. Workshop summaries will be published and collaborative efforts among members are encouraged (e.g., journal articles). Specific issues and agenda topics are determined by the Roundtable membership, and span a broad range of issues relevant to the translation process.

Issues may include the integration and coordination of genomic information into health care and public health including encompassing standards for genetic screening and testing, improving information technology for use in clinical decision making, ensuring access while protecting privacy, and using genomic information to reduce health disparities. The patient and family perspective on the use of genomic information for translation includes social and behavioral issues for target populations. There are evolving requirements for the health professional community, and the need to be able to understand and responsibly apply genomics to medicine and public health.

Of increasing importance is the need to identify the economic implications of using genome-based research for health. Such issues include incentives, cost-effectiveness, and sustainability.

Issues related to the developing science base are also important in the translation process. Such issues could include studies of gene-environment interactions, as well as the implications of genomics for complex disorders such as addiction, mental illness, and chronic diseases.

Roundtable sponsors include federal agencies, pharmaceutical companies, medical and scientific associations, foundations, and patient/public representatives. For more information about the Roundtable on Genomics and Precision Health, please visit our website at nas.edu/genomicsRT or contact Sarah Beachy at 202-334-2217, or by e-mail at sbeachy@nas.edu.

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Roundtable on Genomics and Precision Health

Membership

Sharon Terry, M.A. (Co-Chair) Genetic Alliance
Geoffrey Ginsburg, M.D., Ph.D. (Co-Chair) Duke University

Naomi Aronson, Ph.D.
BlueCross/BlueShield Association

Nazneen Aziz, Ph.D.
Kaiser Permanente

Rebecca Blanchard, Ph.D.
Merck and Co., Inc.

John Carulli, Ph.D.
Biogen

Ann Cashion, Ph.D., R.N., FAAN
National Institute of Nursing Research

Robert B. Darnell, M.D. Ph.D.
NY Genome Center / The Rockefeller University

Michael J. Dougherty, Ph.D.
American Society of Human Genetics

W. Gregory Feero, M.D., Ph.D.
Journal of the American Medical Association

Andrew N. Freedman, Ph.D.
National Cancer Institute

Jill Hagenkord, M.D.
Color Genomics

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Katherine Johansen Taber, Ph.D.
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U.S. Food and Drug Administration

Robert McCormack, Ph.D.
Johnson and Johnson

Jennifer Moser, Ph.D.
U.S. Department of Veterans Affairs

Laura Nisenbaum, Ph.D.
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Eisai Inc.

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Northrop Grumman Health IT

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American College of Medical Genetics and Genomics

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National Society of Genetic Counselors

Robert S. Wildin, M.D.
National Human Genome Research Institute

Janet K. Williams, Ph.D., R.N., FAAN
American Academy of Nursing

Project Staff
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Siobhan Addie, Ph.D., *Associate Program Officer*
Meredith Hackmann, *Research Associate*

To download a free PDF or purchase a copy of the following reports released from the Roundtable on Genomics and Precision Health, please visit the project website at nas.edu/genomicsRT and click on View All Reports from this Activity.

Deriving Drug Discovery Value from Large-Scale Genetic Bioresources – Proceedings of a Workshop
Released: September 9, 2016

Utilizing genetic and phenotypic information collected and stored in bioresources has the potential to enable more efficient drug discovery and precision medicine. Within this context, the Roundtable on Genomics and Precision Health and the Forum on Drug Discovery, Development, and Translation hosted a workshop on March 22, 2016, in Washington DC, titled Deriving Drug Discovery Value from Large-Scale Genetic Bioresources. The workshop focused on new research and ideas in three primary areas: large-scale genetic cohort studies, the use of genomic data in drug discovery activities, and novel business models that support the development and use of genetic data from bioresources for drug discovery. Throughout the workshop there was robust discussion of short-term and long-term opportunities for collaboration, fostering translational research, and accelerating progress in the area of genomic-enabled drug discovery. This publication summarizes the presentations and discussions held at the workshop. The workshop proceedings are available at: https://www.nap.edu/catalog/23601/deriving-drug-discovery-value-from-large-scale-genetic-bioresources-proceedings.

Applying an Implementation Science Approach to Genomic Medicine – Workshop Summary
Released: April 28, 2016

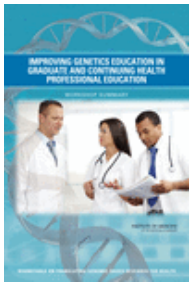
Although it is becoming increasingly more common for clinicians to use genomic data in their practices for disease prevention, diagnosis, and treatment, the process of integrating genomic data into the practice of medicine has been a slow and challenging one. Some of the barriers to the incorporation of this information into clinical practice include the difficulty of changing routine medical practices, patient and provider knowledge about genomic medicine, and assessing sufficient evidence to support the use of genetic tests. Because genomic medicine implementation is still in its early stages, there is an opportunity to use knowledge from other fields to inform best practices and potentially reduce health disparities. The emerging field of implementation science focuses on generating insights that can be applied across settings to promote the uptake of research findings. Recognizing the current challenges that may impede the integration of genomics into clinical practice, the Roundtable on Translating Genomic-Based Research for Health (now called the Roundtable on Genomics and Precision Health) hosted a workshop on November 19, 2015 to explore the methods and approaches of implementation science for their potential ability to improve the integration of genomics into medicine. The workshop focused on the challenges, opportunities, and best practices for integrating genomic medicine into the health care system in a way that addresses the needs of institutions, providers, and patients. This report provides a summary account of the presentations and discussions at the workshop. A summary of this workshop is available at:

http://www.nap.edu/catalog/23403/applying-an-implementation-science-approach-to-genomic-medicine-workshop-summary

Genomics-Enabled Learning Health Care Systems: Gathering and Using Genomic Information to Improve Patient Care and Research - Workshop Summary
Released: May 15, 2015

The sequencing of the human genome has led to a greatly enhanced understanding of the underlying mechanisms of disease. New gene-disease associations are being discovered through a variety of mechanisms and these findings are opening up new possibilities for the identification of therapeutic targets. However, the majority of this information is not being used clinically to inform the treatment of patients due to a lack of evidence regarding the validity of the association and the relationship between specific variants in a particular gene and disease outcome, progression, or prognosis. The inclusion of genomic data in a knowledge-generating health care system infrastructure is one promising way to harness the full potential of genome information to improve health. In such a system, clinical practice and research inform each other with the goal of improving the efficiency and effectiveness of disease prevention, diagnosis, and treatment. To examine pragmatic approaches to incorporating genomics in learning health care systems, the IOM's Roundtable on Translating Genomic-Based Research for Health hosted a workshop on December 8, 2014. A variety of stakeholder groups, including commercial developers, health information technology professionals, clinical providers, academic researchers, patient groups, and government and health system representatives, presented their perspectives and participated in discussions on maximizing the value that can be obtained from genomic information. The workshop examined how a variety of systems are capturing and making use of genomic data to generate knowledge for advancing health care in the 21st century. It also sought to evaluate the challenges, opportunities, and best practices for capturing or using genomic information in knowledge-generating health care systems. A summary of this workshop is available at: http://www.nap.edu/openbook.php?record_id=21707

Improving Genetics Education in Graduate and Continuing Health Professional Education: Workshop Summary
Released: February 6, 2015



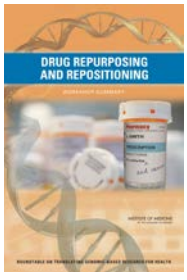
Despite the growing use of genomic applications in clinical practice, health professional knowledge about genomic information and confidence in using it have not kept pace. Genetic influences on health are ubiquitous and multifaceted, which can make it difficult to use this information in a typical health care visit. Many health care providers do not have either the knowledge or the tools they need in order to apply genetic information in their day-to-day practices. This lack of support is contributing to a substantial delay in the translation of genetic research findings, when appropriate, into improvement in patient outcomes within the health care system. The objective of the workshop was to examine the potential and the challenges of providing genetics education, to review promising and innovative approaches to providing education to both graduate health professional

students and practicing health professionals, and to identify potential next steps for achieving effective genetics education. A summary of this workshop is available at: http://www.nap.edu/catalog/18992/improving-genetics-education-in-graduate-and-continuing-health-professional-education

Assessing Genomic Sequencing Information for Health Care Decision Making - Workshop Summary
Released: July 22, 2014

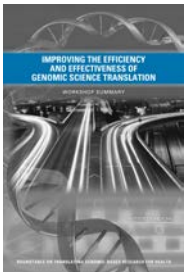
Clinical use of DNA sequencing relies on identifying linkages between diseases and genetic variants or groups of variants. More than 140,000 germline mutations have been submitted to the Human Gene Mutation Database and almost 12,000 single nucleotide polymorphisms have currently been associated with various diseases, including Alzheimer's and type 2 diabetes, but the majority of associations have not been rigorously confirmed and may play only a minor role in disease. Because of the lack of evidence available for assessing variants, evaluation bodies have made few recommendations for the use of genetic tests in health care. Until better evidence becomes available, best practices are needed for making clinical decisions based on genomic information. Identifying these best practices requires understanding how stakeholders gather and evaluate existing genomic evidence to make clinical decisions, develop practice guidelines, and decide whether to cover and reimburse the use of genomic information. On February 3, 2014, the Roundtable on Translating Genomic-Based Research for Health of the Institute of Medicine held a workshop for stakeholders, including clinicians, researchers, patients, and government officials, to discuss how genomic information is gathered, assessed, and evaluated for use in medical practice. A summary of this workshop is available at: http://www.nap.edu/catalog.php?record_id=18799

Drug Repurposing and Repositioning - Workshop Summary
Released: May 22, 2014



Recent estimates suggest that, on average, it takes 10 years and at least $1 billion to bring a drug to market. Given this time and expense, pharmaceutical companies have become increasingly interested in finding new uses for existing drugs – a process referred to as drug repurposing or repositioning. In some cases where data have already been acquired, repurposing a drug can save time and money compared to developing a drug de novo. It has also been estimated that a larger percentage of repurposed drugs gain market approval as compared with drugs developed anew. Advances in genomic technologies and the increasing linkage of molecular information with phenotypic and clinical databases, creates a significant opportunity for genomics to enable drug repurposing. In 2013, the IOM Roundtable on Genomic-Based Research for Health hosted a workshop to assess the current landscape of drug repurposing activities in industry, academia, and government with an emphasis on genomics-based strategies. A summary of this workshop is available at: http://www.nap.edu/catalog.php?record_id=18731

Improving the Efficiency and Effectiveness of Genomic Science Translation - Workshop Summary
Released: May 15, 2014



The low rate of translation of biomedical discoveries from basic science to clinical application has been a source of frustration for many scientists, clinicians, investors, policy makers, and patients who hoped that investments in research could result in improved products and processes for patients. Although understanding of human health and disease biology has increased, the anticipated deliverables from the Human Genome Project have not yet fully materialized and there has not been a consistent increase in approved drugs for patients over the past 10 years. The IOM Roundtable on Translating Genomic-Based Research for Health hosted a workshop to foster collaboration and the exchange of ideas among stakeholders to improve the utilization of genomic research for practical applications. A summary of this workshop is available at: http://www.nap.edu/catalog.php?record_id=18549

Conflict of Interest and Medical Innovation: Ensuring Integrity While Facilitating Innovation in Medical Research - Workshop Summary Released March 21, 2014

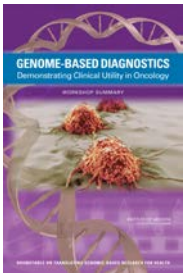
The translation of research advances into clinical applications has been slower than anticipated due in part to the complexity of biology as well as the cost and time it takes to develop a product. Pharmaceutical companies, for example, are adapting their business models to improve the efficiency of product development by putting increasing emphasis on alliances, joint development efforts, early-phase research partnerships, and public-private partnerships. Though the potential benefits of collaboration are significant, the fact that partnerships are becoming more complex with both financial and non-financial relationships, even perceptions of conflict of interest or bias could impact the ability to engage in innovative research collaborations. In June 2013, the IOM Roundtable on Translating Genomic-Based Research for Health held a workshop to explore how to advance medical innovation while protecting the integrity of the research process and maintaining public trust. A summary of this workshop is available at: http://www.nap.edu/catalog.php?record_id=18723

Refining Processes for the Co-Development of Genome-Based Therapeutics and Companion Diagnostic Tests - Workshop Summary Released February 12, 2014

Genomic data can be used to identify new drug targets for both common and rare diseases, can predict which patients are likely to respond to a specific treatment, and have the potential to significantly reduce the cost of clinical trials. Recently, the realization of such benefits has led to the development and approval of several targeted therapeutics. A key component of each of these new drug approvals is the ability to identify the population of patients who will benefit from treatment, which is largely hinged on the co-development and co-submission to the U.S. FDA of a companion diagnostic test. This process has led to a change in the way drugs are developed with pharmaceutical and diagnostic companies working in close collaboration together. In order to discuss

issues in the co-development process, the IOM Roundtable on Translating Genomic-Based Research for Health held a workshop on February 27, 2013. The workshop aimed to examine challenges and potential solutions for the co-development of targeted therapeutics and companion molecular tests for the prediction of drug response. A summary of this workshop is available at: http://www.nap.edu/catalog.php?record_id=18617

Genome-Based Diagnostics: Demonstrating Clinical Utility in Oncology - Workshop Summary
Released November 8, 2013



The sequencing of the human genome has greatly accelerated the process of linking specific genetic variants with disease. These findings have yielded an increasing number of molecular diagnostic tests designed to guide disease treatment and management. Many of these tests are aimed at determining the best treatments for certain cancers, making oncology a valuable testing ground for the use of molecular diagnostic tests in medicine in general. However, many questions surround the clinical value of molecular diagnostic tests and their acceptance by clinicians, payers, and patients has been unpredictable. On May 24, 2012, the IOM Roundtable on Translating Genome-Based Research for Health and the Center for Medical Technology Policy co-hosted a workshop to discuss evidence needs for informed clinical and health policy decision making for molecular diagnostics. The workshop brought together patients, health care providers, policy makers, payers, diagnostic test developers, researchers, and guideline developers, to identify the challenges and opportunities in advancing the development and use of molecular diagnostic tests designed to guide the treatment and management of patients with cancer. A summary of this workshop is available at: http://www.nap.edu/catalog.php?record_id=18275.

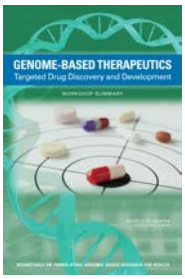
Sharing Clinical Research Data: A Workshop
Released March 29, 2013

Pharmaceutical companies, academics, and government agencies hold large quantities of clinical research data. Much of this information, however, is never published or is statutorily restricted from being made publicly available. Data sharing within and across sectors could facilitate scientific and public health advances and could enhance analysis of safety and efficacy. The Roundtable on Translating Genomic-Based Research for Health and three IOM forums – the Forum on Drug Discovery, Development and Translation, Forum on Neuroscience and Nervous System Disorders, and National Cancer Policy Forum – jointly conducted a public workshop that focused on strategies to facilitate sharing of clinical research data. Participants included members of industry, academia, government agencies such as FDA and NIH, disease advocacy groups, and other stakeholders. The workshop featured invited presentations and discussions that examined the benefits of and barriers to sharing of clinical research data, specifically clinical trial data, and strategies for enhancing sharing within and among sectors to facilitate research and development of effective, safe, and needed products. A summary of this workshop is available at: http://www.nap.edu/catalog.php?record_id=18267.

The Economics of Genomic Medicine - Workshop Summary
Released March 26, 2013

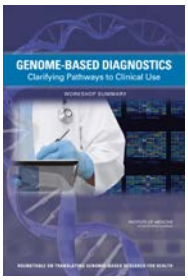
The sequencing of the human genome and the identification of links between specific genetic variants and disease formation have led to an explosion of genomics-based innovation and technology and the advent of genomic medicine. These advancements have the ability to direct patient treatment towards more effective or less harmful options and potentially to reduce health care costs caused by unnecessary or ineffective treatments. However, this is not a certainty and some stakeholders are concerned that genomic technologies will simply be cost additive to the health care system without providing significant benefit to patients. To understand better the health economic issues that may arise in the course of integrating genomic data into health care, the Roundtable hosted a workshop that brought together economists, regulators, payers, biomedical researchers, patients, providers, and other stakeholders to discuss the many factors that may influence this implementation. A summary of this workshop is available at: http://www.nap.edu/catalog.php?record_id=18276.

Genome-Based Therapeutics: Targeted Drug Discovery and Development – Workshop Summary
Released September 5, 2012



The number of new drug approvals has remained steady for the last 50 years while spending on health-related research and development has tripled since 1990. This trajectory is not economically sustainable for the businesses involved, and, in response, many companies are turning toward collaborative models of drug development. Introducing greater efficiency and knowledge into these new models and aligning incentives among participants may help to increase efficiency and lower costs, while producing more effective drugs in the process. Genomic information has significantly increased our understanding of disease and the integration of genome-based strategies into drug discovery and development processes has resulted in the recent successful development of a number of new targeted therapeutics. However, there remains skepticism over how useful genomic information will be to the larger drug development process, requiring examination of the impact of and challenges for incorporating genome-based strategies. The IOM's Roundtable on Translating Genomic-Based Research for Health held a workshop to examine the general approaches being used to apply genome-based research results to the discovery and development of new drugs, the successes achieved so far, and the challenges ahead. A summary of this workshop is available at: http://www.nap.edu/catalog.php?record_id=13436.

Genome-Based Diagnostics: Clarifying Pathways to Clinical Use – Workshop Summary Released March 20, 2012



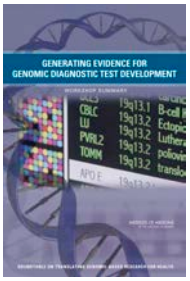
The sequencing of the human genome and the identification of links between specific genetic variants and disease formation have led to an explosion of genomics-based diagnostic tests that have the potential to direct therapeutic interventions or predict onset of disease. However, the current adoption of genomic diagnostic tests into practice by

providers has been limited due to a lack of evidence of clinical utility. Thus, health funders and practitioners lack the data necessary to distinguish which tests can improve practice or the clinical settings in which tests will provide the greatest value. In part, this lack of evidence and usage has led to what has been termed a "vicious cycle" of undervaluation, with test developers producing either no or low evidence of clinical utility, followed by limited usage by providers and little reimbursement by payers. This undervaluation by all groups results in limited resources for developers to produce the evidence desired by various stakeholders and a perpetual continuation of the cycle. The Roundtable on Translating Genomic-Based Research for Health hosted a workshop to identify barriers to genomic diagnostic test development and clinical uptake. The presentations and discussions explored these challenges and identified potential opportunities to advance the development and use of genomic diagnostic tests through research and regulatory policy. Stakeholders including diagnostic test developers, payers, policy makers, health care providers, patient advocacy groups, and others presented their perspectives. A summary of this workshop is available at: http://www.nap.edu/catalog.php?record_id=13359.

Integrating Large-Scale Genomic Information into Clinical Practice: Workshop Summary Released November 11, 2011

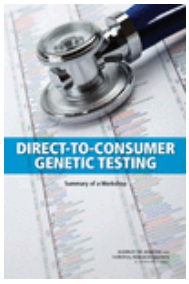
As DNA sequencing technology becomes more refined, costs continue to drop, and clinical applications increase for genomic and genetic analyses, the integration of this new technology into practice is inevitable. However, the large amount of patient-specific data that are generated through large-scale genomic analysis poses a number of questions and challenges for integrating this information into the current health care system. The Roundtable on Translating Genomic-Based Research for Health hosted a workshop to explore and examine potential solutions for integrating large-scale genomic information into clinical practice with respect to the analysis, interpretation, and delivery of genomic information. A summary of this workshop is available at: http://www.nap.edu/catalog.php?record_id=13256.

Generating Evidence for Genomic Diagnostic Test Development: Workshop Summary Released May 6, 2011



Ten years after the sequencing of the human genome, scientists have developed genetic tests that can predict a person's response to certain drugs, estimate the risk of developing Alzheimer's disease, and make other predictions based on known links between genes and diseases. However, genetic tests have yet to become a routine part of medical care, in part because there is not enough evidence to show they help improve patients' health. The IOM held a workshop to explore how researchers can gather better evidence more efficiently on the clinical utility of genetic tests. A summary of this workshop is available at: **http://www.nap.edu/catalog.php?record_id=13133**

Direct to Consumer Genetic Testing: A Cross Academies Workshop
Released December 22, 2010



Dramatic progress in genetic and genomic technologies has ushered in the age of direct-to-consumer marketing of genetic medical testing. Accompanying this new delivery model is a plethora of scientific, medical, legal, and policy issues. Under the auspices of the National Academy of Sciences' Committee on Science, Technology, and Law and Board on Life Sciences and the Institute of Medicine's Roundtable on Translating Genomic-Based Research for Health and National Cancer Policy Forum, a public workshop was held to examine the issues surrounding direct-to-consumer genetic testing. A summary of this workshop is available at:
http://books.nap.edu/catalog.php?record_id=13021

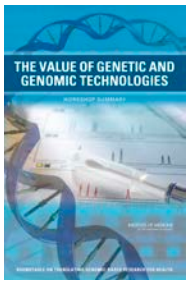
Establishing Precompetitive Collaborations to Stimulate Genomics Driven Product Development: Workshop Summary Released: December 16, 2010

Despite the many basic research discoveries in genetics, relatively few gene-based treatments, drugs, or preventative measures have been developed. One way to bridge this gap may be for industry, academia, and government to develop partnerships that share resources while distributing risk. However, intellectual property protections and other barriers can inhibit collaborative efforts. The IOM's Roundtable on Translating Genomic-Based Research for Health held a workshop on July 22, 2010, to explore these issues and develop solutions. A summary of this workshop is available at:
http://www.nap.edu/catalog.php?record_id=13015

Challenges and Opportunities in Using Residual Newborn Screening Samples for Translational Research: Workshop Summary Released: September 8, 2010

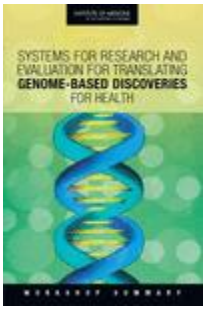
Newborn screening samples are used to test more than 4 million infants each year for life-threatening diseases that are treatable if found at birth. These specimens also represent a potentially invaluable resource for public health and biomedical research. The IOM's Roundtable on Translating Genomic-Based Research for Health held a workshop to examine issues surrounding the use of residual blood samples for translational research. A summary of this workshop is available at:
http://www.nap.edu/catalog.php?record_id=12981

The Value of Genetic and Genomic Technologies: Workshop Summary
Released: August 23, 2010



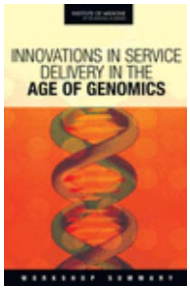
Knowing one's genetic disposition to a variety of diseases, including common chronic diseases, can benefit both the individual and society at large. The IOM's Roundtable on Translating Genomic-Based Research for Health held a workshop on March 22, 2010, to bring together diverse perspectives on the value of genetic testing, and to discuss its use in clinical practice. A summary of this workshop is available at:
http://www.nap.edu/catalog.php?record_id=12947

Systems for Research and Evaluation for Translating Genome-Based Discoveries for Health: Workshop Summary Released: November 11, 2009



The correlation between genetic variation and variations in disease risk has been a subject of study for more than 100 years. Initially, research focused on single genes that give rise to rare genetic diseases such as cystic fibrosis or Huntington's disease. With new studies, however, numerous associations have been found between genes and more common diseases, for example breast cancer, type II diabetes, coronary artery disease, asthma, and bipolar disorder. This rapidly advancing field of genomics has stirred great interest in "personalized" health care. The hope is that using genomic information in care will lead to reduced health care costs and improved health results as preventive measures and treatments are tailored to patients' genetic susceptibilities. On February 12, 2009, the Institute of Medicine's Roundtable on Translating Genomic-Based Research for Health hosted a workshop to examine how to evaluate the clinical use of genomic information and the impact of genetic information in caring for patients. A summary of this workshop is available at:
http://www.nap.edu/catalog.php?record_id=12691

Innovations in Service Delivery in the Age of Genomics: Workshop Summary Released: May 13, 2009



New discoveries in genomics are changing how we diagnose and treat diseases. As the trend shifts from genetic testing for rare genetic disorders to individuals being screened for common diseases, general practitioners, pediatricians, obstetricians/gynecologists, and other providers need to be knowledgeable about and comfortable using genetic information to improve their patients' health. To address these changes, the Roundtable on Translating Genomic-Based Research for Health held a public workshop on July 27, 2008. A summary of this workshop is available at:
http://www.nap.edu/catalog.php?record_id=12601

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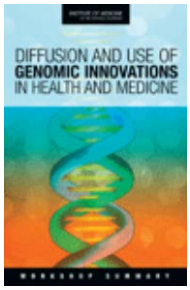
Board on Health Sciences Policy *Roundtable on Genomics and Precision Health*

Diffusion and Use of Genomic Innovations in Health and Medicine: Workshop Summary Released: June 19, 2008



The Institute of Medicine's Roundtable on Translating Genomic-Based Research for Health held a workshop to address the following questions: (1) Are there different pathways by which new scientific findings move from the research setting into health care?; (2) If so, what are the implications of those different pathways for genomics?; and (3) What can we learn from the translation of other new technologies as we seek to understand the translation of genome science into health care? A summary of this workshop is available at: **http://www.nap.edu/catalog.php?record_id=12148**

MEETING INFORMATION

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Board on Health Sciences Policy
Roundtable on Genomics and Precision Health

Spring 2017 Meeting of the Roundtable on Genomics and Precision Health

March 9, 2017

Speaker Biographies

John Barnard, M.D.
John A. Barnard, MD, is chief of Pediatrics at Nationwide Children's Hospital, president of The Research Institute at Nationwide Children's and holds the Ann I. Wolfe Endowed Chair in Pediatric Research Leadership. He is chair of the Department of Pediatrics at The Ohio State University College of Medicine, where he is a professor of Pediatrics in the Division of Gastroenterology, Hepatology and Nutrition. He is also a practicing gastroenterologist in the Division of Gastroenterology, Hepatology and Nutrition at Nationwide Children's. An accomplished physician-scientist, he has authored more than 80 peer-reviewed journal articles, reviews and book chapters and garnered NIH support for more than 2 decades.

As president of The Research Institute, Dr. Barnard is responsible for strategic direction, administration, recruiting, resource allocation and infrastructure design in support of all research activities at Nationwide Children's. The Research Institute is one of the fastest growing pediatric research institutions in the United States and has consistently ranked among the top ten free-standing children's hospitals based on National Institutes of Health funding. In 2015, The Research Institute received more than $90 million in external awards.

As chair of the Department of Pediatrics at Ohio State, he offers counsel, mentorship and oversight for clinical and academic activities of the more than 500 full-time faculty members. He also oversees the education of more than 300 medical students, pediatric residents and fellows training at Nationwide Children's Hospital.

Dr. Barnard received his medical degree from the University of Mississippi and was an intern and resident at the Vanderbilt University School of Medicine, where he also completed a fellowship in pediatric gastroenterology and nutrition. He was a faculty member at Vanderbilt for 11 years, including 5 years as Director of the Division of Pediatric Gastroenterology. He has been named among the Best Doctors in America for the past decade and has served as a past president of the North American Society of Pediatric Gastroenterology, Hepatology and Nutrition (NASPGHAN). He is currently a member of Ohio's Third Frontier Commission and chair of the Ohio Children's Hospital Association Research Collaborative Task Force.

Murray Brilliant, Ph.D.
Dr. Brilliant is a Senior Research Scientist at the Marshfield Clinic Research Foundation and holds the James Weber Endowed Chair in Genetics, where he serves as Director of Research and Director of the Center for Human Genetics. Dr. Brilliant also directs the Personalized Medical Research Project (PMRP) of the Marshfield Clinic. PMRP consists of 20,000+ individuals with long-term (30 year average) electronic health records linked to a biobank of DNA, plasma and serum samples. PMRP has played a key role in the discovery of genetic variants that affect health.

Dr. Brilliant's research team discovered several genes associated with albinism and he is recognized as a leading expert in the genetics of albinism. He serves as Scientific Advisor to the world's largest patient organization on albinism, the National Organization for Albinism and Hypopigmentation. His research group was one of the first to develop predictive algorithms for complex traits (skin, hair and eye color) based on DNA polymorphisms (still used in forensic studies today). With that accomplishment, he began to focus on traits of medical significance, especially eye disorders such as Age-related Macular Degeneration and Glaucoma. Using large sets of patient data, he has shown that L-DOPA apparently protects people from Age-related Macular Degeneration. At the Marshfield Clinic, he has instituted one of the first Clinical Translational Personalized Medicine programs to: 1) identify patients at risk for being prescribed specific drugs (simvastatin, clopidogrel and Warfarin), 2) test those patients for common variants BEFORE they are prescribed these drugs, and 3) implement clinical decision support tools that alert physicians when the prescription is ordered.

Mark Fendrick, M.D.
Dr. A. Mark Fendrick is the Director of the Center for Value-Based Insurance Design and a Professor of Internal Medicine in the School of Medicine and a Professor of Health Management and Policy in the School of Public Health at the University of Michigan. Dr. Fendrick received a bachelor's degree in economics and chemistry from the University of Pennsylvania and his medical degree from Harvard Medical School. He completed his residency in internal medicine at the University of Pennsylvania where he was a fellow in the Robert Wood Johnson Foundation Clinical Scholars Program.

Dr. Fendrick conceptualized and coined the term Value-Based Insurance Design (V-BID) and currently directs the V-BID Center at the University of Michigan [www.vbidcenter.org], the leading advocate for development, implementation, and evaluation of innovative health benefit plans. His research focuses on how clinician payment and consumer engagement initiatives impact access to care, quality of care, and health care costs. Dr. Fendrick has authored over 250 articles and book chapters and has received numerous awards for the creation and implementation of value-based insurance design. His perspective and understanding of clinical and economic issues have fostered collaborations with numerous government agencies, health plans, professional societies, and health care companies.

Dr. Fendrick is an elected member of the National Academy of Medicine (formerly IOM), serves on the Medicare Coverage Advisory Committee, and has been invited to present testimony before the U.S. Senate Committee on Health, Education, Labor and Pensions, the U.S. House of Representatives Ways and Means Subcommittee on Health, and the U.S. Senate Committee on Armed Services Subcommittee on Personnel.

Dr. Fendrick is the co-editor in chief of the American Journal of Managed Care and is an editorial board member for 3 additional peer-reviewed publications. He is also a member of the Institute for Healthcare Policy and Innovation at the University of Michigan, where he remains clinically active in the practice of general internal medicine.

Scott Grosse, Ph.D.
Dr. Scott Grosse has been employed at the Centers for Disease Control and Prevention (CDC) since 1996, where he serves as senior health economist in the National Center on Birth Defects and Developmental Disabilities. Dr. Grosse analyzes data on health services use and costs associated with congenital or neurodevelopmental conditions and associated risk factors. He models health outcomes and economic benefits of public health strategies and policies, such as newborn screening as well as testing

for adult-onset genetic disorders. In addition, Dr. Grosse serves as Federal Advisor to the Condition Review Workgroup for the Advisory Committee on Hereditary Disorders in Newborns and Children (ACHDNC).

Jeffrey Hankoff, M.D.
I have been with Cigna since 2003. I began my Cigna career as Kelly Girl temporary employee medical director and worked my way up to part-time medical director, then full time lead medical director for California, Senior Medical Director, and now Medical Officer. Although officially situated in Glendale, California, I largely work from my home in Santa Barbara, California. My responsibilities include functional oversight nationally of utilization management including precertification, pharmacy, inpatient case management, and core case management. In addition, I have responsibility over our High Profile Case Model, the medical management aspects of our vendor partner relationships, Genetic Testing, Cigna Onsite Health and Total Medical Cost.

Prior to joining Cigna, I was a practicing family physician for over 20 years. I cut my teeth in medical management first as the Chief of Staff at Santa Barbara Cottage Hospital and later as medical director of Santa Barbara Select IPA where I was primarily responsible for utilization management for approximately 25,000 commercial and senior lives. With SBSIPA, I worked closely with two medical management companies – Medical Pathways and later Arcadian. Through Medical Pathways, I also served as medical director for several other medical groups managed by them throughout Southern and Central California.

I completed by undergraduate years in Humanities and Science at MIT and my medical school years at the University of California, Davis. I received my family medicine training at Eastern Maine Medical Center in Bangor, Maine. I have lived in Santa Barbara for nearly 35 years. My wife and I have been married for 39 years. We have two children in their thirties - one an attorney in Los Angeles and the other has recently relocated to Maui with her husband. My non-working time is spent taking care of 2 11-year-old Boston Terriers. I fashion myself somewhat of a fitness freak and have completed 7 marathons including consecutive Los Angeles Marathons over a 5 year period. I no longer run but I have walked with the dogs nearly 10,000 miles over the past 7 years. I enjoy listening to books while walking.

Christine Lu, Ph.D.
Dr. Christine Lu is Assistant Professor and Co-Director of the Precision Medicine Translational Research Center in the Department of Population Medicine (DPM), Harvard Medical School & Harvard Pilgrim Health Care Institute. Her research focuses on policy, ethical, economic and societal issues in precision medicine. She is Multiple Principal Investigator of an NHGRI-funded study to examine ethical and policy implications of access barriers to genomic tests, and Multiple Principal Investigator of a PCORI-funded study to assess the impact of health insurance coverage on patient care and outcomes. She is currently co-leading the Genetic and Molecular Tests Data Workgroup for the Cancer Research Network. Dr. Lu received an Early Career Investigator award from the national Health Care Systems Research Network for her study assessing the impacts of FDA drug warnings on the pediatric population. She received a Caroline Miles Award from Oxford University, UK, for her work on resource allocation and precision medicine.

Eric D. Perakslis, Ph.D.
Eric is currently the Senior Vice President and Head of the Takeda R&D Data Science Institute where he is focused on building a next generation approach to biomedical knowledge infrastructure and culture.

Eric is also a visiting Scientist in the Department of Biomedical Informatics at Harvard Medical School and is a frequent advisor and collaborator to several international aid and relief NGOs.

Most recently, Eric was the Executive Director of the Center for Biomedical Informatics and the Countway Library of Medicine, an Instructor in Pediatrics at Harvard Medical School and is a faculty member of the Children's Hospital Informatics Program at Boston Children's Hospital. While at HMS, Eric focused on the approval of the Department of Biomedical Informatics as a full academic department at HMS, the development of the NIH Undiagnosed Diseases Network, industry collaborations, leading the technology efforts for multiple Ebola response programs, and building active research programs in medical product development, regulatory science and cyber security.

Prior to HMS, Eric was the Chief Information Officer and Chief Scientist (Informatics) at the U.S. Food and Drug Administration. In this role, Eric authored the first IT Strategic Plan for FDA and was responsible for modernizing and enhancing the IT capabilities as well as the *in silico* scientific capabilities at FDA.

Eric has served on the editorial board of *Cancer Today* magazine, on the editorial board and as the Associate Editor for Novel Communications for the DIA flagship publication, the *Journal of Therapeutic Innovation and Regulatory Science*. Eric has also served on several the Advisory Committees for the American Society of Clinical Oncology, the SAB of NuMedii, the leadership team of Precision for Medicine, as the Chairman of the Survivor Advisory Board at the Cancer Institute of New Jersey and as the Chief Information Officer of the King Hussein Institute for Biotechnology and Cancer in Amman, Jordan. Eric has also worked extensively with the LiveStrong Foundation, the Kidney Cancer Association, and the Scientist↔↔Survivor program of the American Association for Cancer Research. Eric has also served as the first CTO for OneMind4Research and as a reviewer for Faster Cures.

Prior to FDA, Eric was Senior Vice President of R&D Information Technology at Johnson & Johnson Pharmaceuticals R&D and was a member of the Corporate Office of Science and Technology. During his thirteen years at J&J, Eric also held the posts of Vice President R&D Informatics, Vice President and Chief Information Officer, Director of Research Information Technology as well as assistant Director and Director of Drug Discovery Research. Prior to J&J, Eric was the Group leader of Scientific Computing at ArQule Inc. and he began his professional career with the Army Corps of Engineers.

Eric has a PhD in chemical and biochemical engineering from Drexel University and also holds B.S.Che and M.S. degrees in chemical engineering.

Michael Snyder, Ph.D.
Michael Snyder is the Stanford Ascherman Professor and Chair of Genetics and the Director of the Center of Genomics and Personalized Medicine. Dr. Snyder received his Ph.D. training at the California Institute of Technology and carried out postdoctoral training at Stanford University. He is a leader in the field of functional genomics and proteomics, and one of the major participants of the ENCODE project. His laboratory study was the first to perform a large-scale functional genomics project in any organism, and has developed many technologies in genomics and proteomics. These including the development of proteome chips, high resolution tiling arrays for the entire human genome, methods for global mapping of transcription factor binding sites (ChIP-chip now replaced by ChIP-seq), paired end sequencing for mapping of structural variation in eukaryotes, de novo genome sequencing of genomes using high throughput technologies and RNA-Seq. These technologies have been used for characterizing genomes,

proteomes and regulatory networks. Seminal findings from the Snyder laboratory include the discovery that much more of the human genome is transcribed and contains regulatory information than was previously appreciated, and a high diversity of transcription factor binding occurs both between and within species. He has also combined different state-of–the-art “omics” technologies to perform the first longitudinal detailed integrative personal omics profile (iPOP) of person and used this to assess disease risk and monitor disease states for personalized medicine. He is a cofounder of several biotechnology companies, including Protometrix (now part of Life Technologies), Affomix (now part of Illumina), Excelix, and Personalis, and he presently serves on the board of a number of companies.

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Board on Health Sciences Policy
Roundtable on Genomics and Precision Health

Spring 2017 Meeting of the Roundtable on Genomics and Precision Health

Speaker Guidelines

Thank you for agreeing to speak at a session of the Mobile Health (mHealth) and Genetics/Genomics Interest Group at our upcoming Genomics Roundtable meeting on March 9, 2017 in Washington DC. The mHealth Interest Group is interested in exploring how mHealth technologies can be utilized to enable precision health, improve research (e.g., patient reported outcomes, continuous phenotypes), and in turn, clinical care (e.g., monitoring, feedback, adherence, etc.). On March 9, the Roundtable would like to learn more broadly about the opportunities and challenges that exist for integrating mHealth applications/tools into clinical care. The group would also like to determine what activities the Roundtable can undertake to help positively impact the field.

The objectives of this session are:

- To examine the major challenges that surround the design of mHealth applications and the collection of highly complex data for research and clinical care, including data quality and analytics, privacy/security, data ownership, and patient consent processes.
- To learn how mHealth applications that include genomic and EHR data could fit into the clinical workflow.

Twelve (12) minutes have been allotted for your presentation and we request that you consider the questions for your session below as you prepare. Following the session presentations, there will be time for an in-depth discussion with Roundtable members.

If you choose to use slides, please send your presentation to **Meredith Hackmann** (mhackmann@nas.edu) by **Monday, March 6, 2017.** Please also send any relevant background articles or resources to Meredith by **February 24, 2017**, for inclusion in a briefing book that will be prepared for members and speakers.

If you have any questions about your session, please feel free to contact **Siobhan Addie** (saddie@nas.edu). Thank you and we look forward to seeing you soon.

Speaker Guidance Questions

Session II – Intersection of Genomics and Precision Health and mHealth

Speakers: Michael Snyder and Eric Perakslis

Moderators: Ann Cashion and Geoff Ginsburg

1. What technical barriers do you foresee in integrating mobile health (mHealth) data into the clinical workflow? How can developers ensure that mHealth apps integrate with each other to be most effective for clinicians and patients?
2. How can mHealth apps provide value/ROI for health care overall and genomics specifically?
3. Have you found that clinicians and patients/participants are supportive of mHealth efforts?
4. What are your views and/or how do you approach data sharing and data ownership? What do you find to be most successful in terms of engagement and research?
5. Are there specific challenges related to apps that collect genomic information? If so, what privacy/security questions must be addressed?
6. How are you managing issues related to access and health disparities?

7. What elements do you see as necessary in making the mHealth to clinic vision a reality? Are there incremental steps that can be taken now to lay the groundwork? What do you believe will be truly innovative/transformative?

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Board on Health Sciences Policy
Roundtable on Genomics and Precision Health

Spring 2017 Meeting of the Roundtable on Genomics and Precision Health

Speaker Guidelines

Thank you for agreeing to speak at a session of the Public Health Systems and Implementation Interest Group at an upcoming Roundtable meeting on March 9, 2017, in Washington, DC. The interest group members would like to explore issues that pertain to the return on investment of genomic medicine-based approaches. In this instance, genomic medicine can encompass a number of different scenarios. Examples of genomic medicine include tumor gene expression profiling, cascade screening in first-degree family members of a patient with a hereditary cancer syndrome, screening for a genetic variant that causes hypersensitivity to a particular drug, and personalized genetic tests that are available direct to consumers. For the purpose of this session, the term return on investment includes financial outcomes, patient outcomes, and the quality of care.

The interest group members would like to gather more information more about the types of analyses that payers, health care systems, and public health departments utilize to assess the return on investment of genetics and genomics-based tests and services. The session was designed to include wide-ranging perspectives including: those of payers, health economists, and leaders of health care delivery systems.

As part of your presentation we would like you to inform Roundtable members about your work, discuss gaps and opportunities, and help us explore ways for the Roundtable members to perform impactful work in this space.

Twelve (12) minutes have been allotted for your presentation and we request that you address the questions below during your presentation. Following the session presentations, there will be at least 30 minutes for an in-depth discussion with the Roundtable members.

If you choose to use slides, please send your presentation to **Meredith Hackmann** (mhackmann@nas.edu) by **Tuesday, March 7.**

If you have any questions about your session, please feel free to contact **Siobhan Addie** (saddie@nas.edu). Thank you and we look forward to seeing you soon.

Speaker Guidance Questions

Session II – EXPLORING RETURN ON INVESTMENT OF GENOMIC MEDICINE

Speakers: John Barnard, Murray Brilliant, Mark Fendrick, Jeffrey Hankoff, Scott Grosse

Moderators: Sam Shekar and Sheri Schully

1. What are the current approaches used by payers and health care delivery systems to determine the return on investment of genomic medicine tests/services?
    a. Are there specific economic models or frameworks that can be utilized to forecast the costs/benefits of genomics-based approaches before, during, and after implementation?

   b. What are the best ways to measure value, personal utility, and patient preferences regarding genomic/genetic tests?
   c. Are there other examples that you can think of outside of genomics that would provide useful lessons on how to measure return on investment?
2. How do new models of care (e.g., value-based purchasing approaches, including provider shared savings) impact the economic incentives for test and evidence development related to genomic medicine programs?
   a. How does innovation, or the development of new technologies, play a role in this process?
3. If a health care system has grant support to run a genetics program/test/service, and is able to develop a strong evidence base, what are the effects of subsequently losing external grant support? How can health care systems continue programs and/or leverage existing resources in the face of reduced funding?
4. What role do patients have in the utilization of genetic tests/services?
5. What are the current methods used to compare outcomes following implementation of genomics-based programs?
   a. How can one compare the cost-effectiveness of different clinical interventions (e.g., using cascade screening to identify cases of familial cancer)?
6. What types of research studies are needed to show the return on investment of genetic tests/services?

BACKGROUND ARTICLES

Research Article

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Personalized Medicine

Strategies for integrating personalized medicine into healthcare practice

Aim: Research and innovation in personalized medicine are surging, however, its adoption into clinical practice is comparatively slow. We identify common challenges to the clinical adoption of personalized medicine and provide strategies for addressing these challenges. **Methods:** Our team developed a list of common challenges through a series of group discussions, surveys and interviews, and convened a national summit to discuss solutions for overcoming these challenges. We used a framework approach for thematic analysis. **Results:** We categorized challenges into five areas of need: education and awareness; patient empowerment; value recognition; infrastructure and information management; and ensuring access to care. We then developed strategies to address these challenges. **Conclusion:** In order for healthcare to transition into personalized medicine, it is necessary for stakeholders to build momentum by implementing a progression of strategies.

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Keywords: access to care • clinical adoption • information management • integration into healthcare • patient empowerment • personalized-medicine education • value determination

Daryl E Pritchard*[,1], Franziska Moeckel[2], Mary Susan Villa[3], Laura T Housman[4,5], Catherine A McCarty[6] & Howard L McLeod[7]

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Personalized medicine is an evolving field in which physicians use diagnostic tests to identify specific biological markers, often genetic, that help determine which medical treatments and procedures will work best for each patient. By combining this information with an individual's medical records and circumstances, personalized medicine allows doctors and patients to develop targeted treatment and prevention plans [1,2]. While there are many alternative terms for personalized medicine, including precision, individualized and stratified medicine, this report does not distinguish between those terms or attempt to reconcile differing definitions of each. Rather, the term personalized medicine is used throughout the report to describe the concept as defined above.

Research and innovation in personalized medicine are extensive and expanding, as measured by the number of scientific publications and a documented emphasis on genetic testing, health information management, biomarker discovery and targeted therapies [3,4]. The molecular diagnostics market is growing rapidly and diversifying. A recent report by NextGxDx estimated that nearly 4000 new diagnostic tests have been introduced to the market in 2015 [5]. The same can be said for the molecular therapeutics market. In fact, 28% of all the medicines the US FDA approved in 2015 were personalized medicines [6], and a recent study sponsored by the Personalized Medicine Coalition (PMC) and conducted by Tufts University demonstrates that 42% of all medicines and 73% of cancer medicines in development are potential personalized medicines [7].

However, despite the steady increase in the number of clinically useful molecular diagnostics and targeted therapies, the healthcare system has been slow to integrate personal-

Future Medicine part of fsg

ized medicine into clinical practice [8–10]. Indeed, evidence suggests that in most cases, personalized medicine is not even discussed at the point of care. A recent public survey has shown that only four out of ten consumers are aware of personalized medicine, and only 11% of patients say their doctor has discussed or recommended personalized medicine treatment options to them [11]. Behind this lag in clinical adoption are novel challenges that healthcare delivery systems are encountering as they adapt to the new requirements, practices and standards associated with the field [12].

Background

Since the completion of the Human Genome Project in April 2003, there has been an increasing focus on genomics in medicine, coupled with efforts to help incorporate genomic information into healthcare practice. The US CDC established the Evaluation of Genomic Application in Practice and Prevention program in 2005 to evaluate genetic tests and other applications of genomic technology in transition from research to health practice [13]. The Human Genome Research Institute's Implementing Genomics in Practice Network addressed barriers to the integration of genomics into medicine and offered potential solutions [14], and the Electronic Medical Records and Genomics Network has addressed the uptake of genetic information in electronic health record systems for genomic discovery and genomic medicine implementation research [15]. The Clinical Genome Resource is currently developing interconnected community resources to improve understanding of genomic variation and its use in clinical care [16]. At the National Academy of Sciences, Engineering, and Medicine, an Institute of Medicine Roundtable on Translating Genomic-Based Research for Health issued workshop reports on "Integrating Large-Scale Genomic Information into Clinical Practice" [17] and "Genomics-Enabled Learning Health Care Systems: Gathering and Using Genomic Information to Improve Patient Care and Research" [18]. While this report focuses primarily on US healthcare institutions, clinical adoption of personalized medicine is advancing globally. For example, the Personalized Medicine 2020 and Beyond Strategic Research and Innovation Agenda included the development of an index of barriers for the implementation of personalized medicine and pharmacogenomics in Europe [19]. Most recently, the Pharmacogenomics Knowledgebase and the Pharmacogenomics Research Network established the international Clinical Pharmacogenetics Implementation Consortium to help develop updated pharmacogenomics clinical practice guidelines [20].

While these programs have facilitated a dialogue about how to incorporate genomic information into healthcare practice, recent surveys show that most healthcare organizations are unprepared to implement personalized medicine [21] and some hospital systems may be putting implementation programs on hold [22]. The barriers often involve knowledge gaps, system-wide process obstacles and resistance to the cultural changes necessary to move toward a more personalized care paradigm. Often, personalized medicine programs are working in isolation and therefore are not benefitting from the experiences of other healthcare delivery organizations.

PMC's Healthcare Working Group (HWG) has identified common challenges involved in developing personalized medicine programs and the most promising strategies for addressing them. This article describes this initiative, which has provided a forum for healthcare delivery organizations to discuss integration of personalized medicine into clinical practice, highlighted basic principles, identified integration challenges, developed corresponding strategies to address challenges and outlined a roadmap to help foster cultural change in medical practices.

Methods

PMC's Healthcare Working Group

PMC's HWG is comprised of representatives from 49 organizations involved in healthcare delivery, including 19 academic health centers, 12 community healthcare systems, 16 healthcare delivery support organizations and two physician groups (Supplementary Material 1).

PMC conducted a survey of the HWG regarding concerns and challenges related to the development and implementation of personalized-medicine strategies in clinical practice. From that survey the group developed a set of principles and a list of significant common challenges encountered by healthcare delivery organizations. PMC then conducted semi-structured interviews with senior executives to provide details and distinguish the most significant challenges faced by providers of all types. The group reviewed and revised the principles and list of challenges through a series of teleconference discussions. Finally, PMC used a framework approach of qualitative research for thematic analyses.

Solutions

PMC coordinated a series of focus group discussions to discuss potential solutions for addressing the identified common challenges. The sessions included three separate discussions representing different stakeholders – providers (17 participants), industry (23 participants) and patients (14 participants). Focus group members

participated on a volunteer basis. No compensation, individual or organizational attribution in this or any publication was provided. Each group answered a series of questions about strategies for addressing common challenges (see Supplementary Material 2 for a list of focus group questions). From the responses, PMC developed a list of strategies to tackle each challenge. Alongside its partner, the Biotechnology Innovation Organization, PMC then hosted a national meeting – Solutions Summit: Integration of Personalized Medicine into Health Care – on 14 October 2015, to discuss and refine the list of solutions. The Solutions Summit was sponsored in part by corporate and nonprofit organization partners: Alliance for Aging Research, AstraZeneca, CareDx, Foley Lardner LLP, Foundation Medicine, Johnson & Johnson, The National Pharmaceutical Council, Novartis, Pfizer and Vertex.

Results

Members of the HWG broadly reported that healthcare delivery systems are encountering novel challenges as they adapt to the new requirements and practices associated with personalized medicine. They identified five general areas of challenges:

- Education and awareness;
- Patient empowerment;
- Value recognition;
- Infrastructure and information management;
- Ensuring access to care.

The group developed five principles for integrating personalized medicine into healthcare that correlate with each of these areas (Box 1). Various previous efforts to better understand and prioritize challenges to integrating personalized medicine into healthcare have identified similar categories. For example, in Europe and Canada, the Personalized Medicine 2020 and Beyond Strategic Research and Innovation Agenda categorized barriers to clinical adoption in the areas of stakeholder involvement; standardization; interoperable infrastructure; healthcare system; data and research; funding; and policy making [23].

Certain obstacles are particularly common among healthcare delivery organizations. The HWG identified the most significant of these and assigned them to five categories corresponding with the five identified areas of need (Box 2). It is noted that the perspective, scope and magnitude of specific integration challenges sometimes differ between distinct types of healthcare delivery organizations, such as academic health centers and community hospitals. Thus, the HWG did not prioritize individual challenges, but rather emphasized that all of the common challenges are significant barriers to the integration of personalized medicine into clinical practice and identified the overarching priority as recognizing and addressing the need for a paradigm shift from traditional practice to personalized medicine.

Box 3 lists strategies organizations have implemented in part or in full to overcome the integration challenges. Organizations believe these strategies can be expanded nationally. The solutions are listed in categories corresponding with the five general areas of need. However, more specific descriptions of challenges were necessary to help provide clearer direction for potential action on particular solutions. These strategies are not meant to imply that healthcare delivery organizations must act alone in their implementation. On the contrary, many of the strategies involve developing evidence, building resources and/or partnering on policy activities with multiple stakeholder groups. The need for these collaborative solutions reflects perceived shortcomings

Box 1. Principles for integrating personalized medicine into healthcare.

- Personalized medicine is a fundamental change in the way medicine is practiced and delivered. It strengthens prevention, diagnosis and therapeutic efforts through customized treatments appropriate for each patient. In order to integrate personalized medicine into healthcare practice, the following principles should be considered:
  - Healthcare providers, payers, employers and policymakers, as well as patients and their families, need to have a better understanding of personalized medicine concepts and technologies
  - Policies and practices related to patient engagement, privacy, data protections and other ethical, legal, and societal issues regarding the use of individual molecular information must ensure appropriate consent and be acceptable to patients
  - Best practices must be established for the collection and dissemination of evidence needed to demonstrate clinical utility of personalized medicine and ensure the recognition of its value to care
  - Effective healthcare delivery infrastructure and data management systems should be developed and applied so that individual patient and clinical support information is comprehensive, useful and user friendly, and so that it can be used to guide clinical decisions
  - Best practices for healthcare delivery approaches, processes and program operations that ensure access to personalized medicine must be established and implemented

Box 2. Common challenges to integrating personalized medicine into healthcare.

Awareness & education

- Variable terminologies exist for personalized medicine, leading to confusion
- Consumer awareness is poor, and demand for products and services is relatively low:
  - The science is complex and often difficult to correlate with various personalized treatment options
  - Different consumers have different information needs and health literacy levels
- Awareness and knowledge within the healthcare provider community is insufficient:
  - Knowledge resources are scarce, seldom used and are not regularly updated
  - Education efforts outside of oncology are uncommon
- Information on personalized medicine practices, policies and community support is not readily available, or not being used
- Workforce training for new technologies/techniques is insufficient
- Medical school curricula on integrating genetics/genomics are often outdated

Patient empowerment

- Patient consent policies for the use of molecular information are often confusing or inappropriate
- Molecular information is often not secure and may be subject to hacking
- Data sharing policies do not always take into consideration proprietary or privacy concerns
- Providers do not adequately involve patients in their healthcare decision-making, and do not account for the level that a patient wants to be engaged in healthcare discussions:
  - Patient preferences in treatment and prevention strategies are not always considered
- Patients and their families are often not appropriately counseled with regard to genomics
- Racial, ethnic, economic and regional disparities are not appropriately addressed

Value recognition

- It is unclear what evidence payers require to facilitate coverage
- Payment rates for diagnostics are often not based on their value to care
- Clinical and economic data demonstrating value are still emerging
- It is unclear what evidence is necessary to convince doctors to clinically adopt new technologies and services:
  - Not all molecular variants are clinically actionable
  - Practice guidelines are slow to be updated
- Healthcare organizations do not recognize the value of integrating personalized medicine to the institution:
  - The return on investment across the institution is not yet clear
  - Programmatic value that may not have an immediate return on investment is not well understood
- Preventive care is often overlooked in practice
- There are few incentives for sharing clinical data that could enhance the understanding of value, such as individual variability and outcomes data

Infrastructure & information management

- Personalized medicine programs lack clear decision-making processes
- Policies and processes are not always coordinated across the healthcare institution:
  - Communication across the continuum of care is insufficient or breaks down easily
  - Molecular information is not often coupled meaningfully within clinical support tools
  - Research is not well coordinated with clinical practice
  - Policies to better evaluate program efficiency and to implement adjustments are lacking
  - Laboratory services often operate in a silo
- It is unclear what diagnostic tests can/should be run in-house versus being sent to external laboratories
- Source factors are often not appropriately considered when making decisions regarding buying versus making diagnostic tests:
  - Projection of product volumes may be inaccurate considering new diagnostic and therapeutic needs
- Information technology systems/platforms are unable to effectively manage exceptionally large amounts of individual molecular information
- Molecular information collection, storage and analysis take more time than many physicians feel it is worth
- Electronic health record information is not standards based and usually not interoperable
- Individual molecular data are not effectively translated into evidence for clinical care
- Biorepositories are often not effectively maintained or integrated with information systems

Ensuring access to care

- Many high-value diagnostic tests or services are not covered by health insurance companies
- Traditional fee-for-service processes provide a system-wide incentive for ordering services based on volume rather than value
- Electronic health records do not easily incorporate genetic information

Box 2. Common challenges to integrating personalized medicine into healthcare (cont.).

Ensuring access to care (cont).

- Some physicians are reluctant to adopt personalized medicine practices:
  - There is a perception that personalized medicine techniques require time without adequate compensation
  - There is a perception that it is too cumbersome to involve genetics experts/counselors in patient care
- Clinical guidelines do not reflect current concepts in personalized medicine
- Most clinical decision support tools are not equipped for integrating patient biomarker information in treatment decision-making
- Serious adverse events/US FDA black box warnings related to targeted treatments are often misunderstood related to use in appropriate populations
- Medical groups, community healthcare organizations and other outside stakeholders are often not coordinated with regard to personalized medicine programs and guidelines
- Sustainable business models are yet to be developed
- Products and services are not always available, particularly in rural settings, and many patients are reluctant or unable to travel to other health centers
- Geneticists/genetic counselors/molecular pathologists are not always accessible, especially in rural settings

of the current medical practice paradigm in which separate institutions advance priorities independently. These strategies thereby underline the need for a new paradigm.

Discussion

The evolution of healthcare delivery to personalized medicine requires making new knowledge available, placing a greater emphasis on patient perspectives, recognizing the value of molecular pathways in guiding care, building new infrastructure and information management processes and reshaping healthcare delivery to ensure access to personalized medicine technologies and services. Overcoming challenges in these areas will likely require near-term strategies to implement programs that are straightforward and can provide clear solutions as well as long-term strategies that can drive systemic and cultural change. However, with a clear understanding of the set of challenges and the best strategies for overcoming those challenges, a roadmap for healthcare systems to advance the personalized medicine paradigm can be built.

Education & awareness

Perhaps the greatest challenge to integrating personalized medicine into healthcare is a lack of education and awareness among patients and throughout the healthcare delivery community. The path forward in this area, however, might be the clearest and most straightforward. Freely available educational resources that provide necessary basic scientific explanations of personalized medicine principles as well as technology-specific details have been and are being developed by a number of organizations [24–28]. When published online, these materials can be presented in multiple formats based on the needs of different stakeholders. However, they must be accurate, trusted and updated regularly. PMC continues to work with the personalized medicine community to develop a content-rich website that can serve as the 'go-to' source for personalized medicine knowledge [29]. Other strategies to address education challenges include coordinating community forums to agree upon a common terminology regarding personalized medicine and to engage community leaders as well as patient support groups and healthcare delivery professionals to help promote personalized medicine and disseminate educational materials.

Although many community education strategies are clear, building awareness and knowledge will not be easy, especially with regard to physicians and other healthcare providers. In-person training and educational programs led by genetic experts can be made available that help ensure that provider's knowledge is up-to-date regarding personalized medicine. Current medical and pharmacy school curricula can also be updated to reflect current medical concepts. While reaching an adequate level of awareness and education among all stakeholders will take time, strategies to address these challenges are straightforward and ready for implementation.

Patient empowerment

As we move forward, patients can be fully informed, both in terms of options for prevention or treatment of disease and efforts to protect their molecular information from being used in ways that would cause them concern, and perhaps, long-term repercussions, such as discrimination, job loss or loss of health insurance coverage. Patients can be involved in deciding how their data are used, particularly in an environment where care is managed across a number of specialized physicians (i.e., oncologist, cardiologist and rheumatologist, among others).

In these areas too, the way forward seems clear. Many health and research organizations in the public and pri-

vate sectors are reconsidering current policies related to patient privacy and consent for the use of molecular information, such as the development of updated recommendations and policies on informed consent for participation in clinical research [30–32]. Some providers are developing genetic counseling service policies

Box 3. Strategies for overcoming challenges to integrating personalized medicine into healthcare practice.

Awareness & education

- Challenge: healthcare providers, payers, employers and policy-makers, as well as patients and their families, often have a poor or impractical understanding of personalized medicine:
  - Develop freely accessible online educational information that is presented in multiple formats based on the needs of different stakeholders
  - Organize collaborative forums to develop and agree upon a common lexicon regarding personalized medicine
  - Organize industry forums to develop and agree upon consistent themes for communications based on scientific evidence and value
  - Provide healthcare professional groups and patient support organizations with personalized medicine information and educational materials, and actively manage multiple communication and dissemination channels
  - Identify physician and community leaders to participate in regional events that raise awareness and promote personalized medicine
  - Engage pharmacists to help patients understand the molecular mechanisms of their disease and the benefits of personalized medicine technologies
  - Develop social media platforms to raise awareness of personalized medicine events, activities and new technologies
  - Update the current medical and pharmacy school curricula to holistically integrate concepts related to personalized medicine
  - Develop new personalized medicine Continuing Medical Education programs

Patient empowerment

- Challenge: patients need to be proactively involved in their treatment decision-making, and in policy development related to information privacy, data protections and other ethical, legal and societal issues:
  - Include patient representatives in the development of proactive policies and practices related to patient protections and the use of individual molecular information
  - Implement state-of-the-art cybersecurity measures related to individual molecular information
  - Develop programs to explain diagnostic test results to patients; provide them with recommendations and easy access to related information and counseling
  - Provide counseling services to patients before ethical dilemmas arise
  - Incorporate patient-reported outcomes through multiple channels to capture and better understand patient experiences
  - Design clinical trials with diverse research participants that include persons of various ethnicities, races, ages and genders to better inform the value of a specific treatment option for any given patient

Value recognition

- Challenge: payers and providers are unconvinced of the benefits of personalized medicine; evidence demonstrating its value to healthcare is still emerging:
  - Provide a forum for payers and the diagnostic and biopharmaceutical industries to discuss the health technology assessment process and evidence requirements necessary for coverage
  - Conduct economic impact studies that are meaningful to payers
  - Design clinical studies to serve multiple purposes, including regulatory approval, establishing clinical utility for payers and informing clinical guidelines; customize scientific and value-based evidence reports for different audiences (payer, provider, clinical guideline developers) based on their particular needs
  - Develop standards as well as measurable targets for comparative effectiveness research studies and coverage with evidence development programs
  - Design and implement research studies that demonstrate the cost and benefits of positive coverage decisions in areas of unmet need
  - Develop and implement proactive policies that incentivize healthcare providers for optimizing treatments based on individual patient characteristics
  - Include medical center and in-house provider laboratories in US Center for Medicare and Medicaid Services median pricing determination for a fairer market value for diagnostic tests
  - Facilitate a learning health system by developing an effective, universally accepted and user-friendly process to systematically collect and share treatment and outcomes data

Box 3. Strategies for overcoming challenges to integrating personalized medicine into healthcare practice (cont.).

Infrastructure & information management

- Challenge: health system infrastructure and information management are not yet well equipped for handling the massive amounts and different kinds of information associated with personalized medicine:
  - Coordinate institutional policies and processes that assure effective communications through the continuum of care and across research and clinical programs, and develop an effective process for making programmatic decisions
  - Include each patient's individual genetic data, as well as information regarding clinically actionable variants, within electronic health records
  - Assure that all medical data, clinical support and outcomes information are standardized and interoperable across multiple health information technology platforms
  - Develop and implement user-friendly platforms to input data, and provide clinical support information to physicians in a way that saves time and resources
  - Develop platforms that are easily customized for different clinicians based on the level of information that best suits them
  - Assure that clinical support information includes complicating factors such as previously failed treatment classes and contraindications, and is provided within the electronic health record in a way that is easily recognized and accessed by physicians
  - Incorporate adverse event reporting and link it to pharmacogenetic information on an individual and population-wide basis
  - Develop proactive policies to incentivize data sharing and facilitate real-time data exchange for learning health systems

Ensuring access to care

- Challenge: healthcare systems processes and procedures are optimized for traditional trial-and-error and fee-for-service practices resulting in disincentives for the use of personalized medicine products and services:
  - Develop incentives for payers to cover novel technologies with value-based evidence accumulation
  - Develop policies that ensure clinical guidelines and support tools are focused on providing the best treatment strategies for individual patients and are regularly updated.
  - Develop policies that remove disincentives for using technologies that are high value but are provided outside of network laboratories
  - Ensure that professional fees for personalized medicine services and biomarker variant analyses are adequate
  - Ensure access to genetic analysis experts and counselors where appropriate (including virtual access when necessary) and that streamline the process for their inclusion in patient care
  - Develop and implement a healthcare system-wide approach to basket-studies/clinical trial enrollment based on molecular characteristics
  - Include personalized medicine principles and practices in alternative payment and delivery models

to ensure that patients, early in their care, are able to understand their individual molecular information and its implications, so that they are able to make informed decisions regarding its disclosure and use before problems arise [33–35]. Additionally, programs are being developed or are ready to be implemented that will establish the necessary partnerships among industry suppliers, providers, and patients and their families to ensure patient data are presented in ways that are meaningful and useful to each of these groups. Perhaps most importantly, practitioners are recognizing that they need to regularly and appropriately involve patients in their ongoing healthcare decision-making [36]. Indeed, practitioners are increasingly recognizing that they have a duty to do so. Health systems can provide the necessary educational and consultation support that makes that possible, and information systems can be designed to ensure an appropriate role for patients.

Value recognition

While many stakeholders believe that personalized medicine can provide benefits to patients and the healthcare system, payers and providers are often reluctant to change policies and practices without convincing evidence of clinical and economic value [3]. It is not clear how that evidence should be developed and disseminated for maximum impact. It is also not clear to healthcare delivery organizations how to develop profitable business models to support and sustain the delivery of personalized medicine.

However, strategies to include economic and clinical risk reduction end points within the body of evidence, in addition to patient survival and disease progression information, have begun to emerge and are much needed. Forums between payers and product developers, for example, may facilitate a better understanding of the evidence requirements necessary for positive

coverage determinations. When generating evidence reports, product manufacturers can customize them for different audiences, such as payers, providers and clinical guideline developers. However, the personalized medicine value proposition increasingly depends on provider evidence generation. Providers decide which products and services to use and frequently must negotiate with payers to procure insurance coverage. The evidence that payers require to make coverage determinations for diagnostic tests is increasingly generated through analysis of clinical practice data. Thus, providers may consider collaborating directly with manufacturers and payers as part of a three-pronged approach to value determination.

To help facilitate an understanding of how personalized medicine can affect patient care, providers can establish proactive policies that incentivize practitioners to optimize treatments based on individual patient characteristics. However, as with insurance coverage, the facilitation of incentives for the delivery of personalized treatments will likely require practice-based evidence about their value. The need for evidence to facilitate policies that allow greater access to personalized medicine, contrasted with the need for access policies that enable evidence generation, has led to a challenging conundrum in demonstrating the value proposition. Both payers and providers would benefit from the implementation of a learning health system that provides a universally accepted and user-friendly way to systematically collect and share treatment and outcomes data. Implementing a learning health system would benefit from effective information management systems to aggregate and easily share clinical data for all patients, so as to analyze common patterns.

Infrastructure & information management

Effectively managing the massive amounts of information associated with personalized medicine and coordinating programmatic processes and services related to its use are also major areas of need. Many organizations are committed to overcoming challenges in these areas, but strategies need to be developed and implemented widely in order to have a meaningful impact on the larger healthcare system. Combining efforts can start by fostering a better understanding of different perspectives across stakeholder groups, encouraging more structured collaborations, and sharing experiences and best practices among healthcare organizations. Healthcare delivery organizations that have implemented personalized medicine programs and are working with information management organizations highlight the need for clear program leadership structures, effective processes for making programmatic decisions, and coordination of institutional personalized medicine program policies and processes across research and clinical programs. In consideration of this, improvements to electronic health records can be developed and implemented so that they include individual patients' genetic information with built-in clinical support tools, describing potential clinical actionability. Biomarker and outcomes information can be standardized and interoperable across multiple health information technology platforms.

Ensuring access to care

Perhaps the most complex area of need is adapting health delivery approaches, processes and service structures to ensure access to personalized medicine. In many cases, overcoming challenges in this area requires cultural change as well as the implementation of new programs. Progress will likely require the shifting of the perspectives of many stakeholders toward a personalized medicine paradigm, which can be accelerated by improving the knowledge base, empowering patients, demonstrating value across stakeholder groups, and building effective program infrastructure and information management processes. Traditional fee-for-service practices can sometimes provide incentives for providers to deliver increased service volumes rather than identifying the best interventions for particular patients. Payer, provider and patient-directed policies to promote cultural change, such as developing incentives for payers to cover novel personalized medicine technologies with value-based evidence accumulation and defining value in terms of patient outcomes, could help accelerate progress. Guidelines and clinical support tools that are focused on the best care for individual patients can be regularly updated to include personalized medicine concepts and practices. Other practical strategies needed to begin breaking down the cultural barriers to personalized medicine, include removing disincentives for using new technologies that are of high value but are provided outside of network laboratories and making sure that professional fees for personalized medicine services and biomarker analysis are appropriate, both for the practitioner and the payer. Implementing these strategies will not suddenly change ingrained medical practice norms and culture, but will help contribute to an accelerating paradigm shift toward personalized medicine.

Study limitations

The strategies and recommendations listed in this report are generalized to all US healthcare delivery organizations and do not account for regional differences in care delivery or distinguish between academic health centers and community hospital systems. The primary differences between academic health cen-

ters and community hospitals are the availability of resources and the nature of institutional missions. Academic health centers often include both research and education in their missions and often have endowments and/or research grants. In these settings, support of research activities is recognized as vital to the delivery of high-quality healthcare. In contrast, community hospitals rarely include research and education in their missions and there can be a tension between research endeavors and clinical care. In these settings, the research programs that do take place typically favor translational research that will benefit a specific patient population and it can be difficult to attract external funding. Thus, it is important to consider the type of healthcare institution being evaluated when considering the strategies and recommendations presented here. For example, community hospital systems often ranked workforce education as a higher priority challenge than many academic health centers. Also, it is important to consider the regional context for the delivery of care. The types of challenges and their magnitude of impact on the adoption of personalized medicine can differ between urban and rural settings. For example, in some rural areas, the lack of access to high-speed internet continues to challenge education, e-learning and e-health programs, and adoption lags behind internet availability [37]. There is also a growing rural/urban divide on compliance with "meaningful use" requirements pertaining to medical records [38]. A description of specific case examples of various healthcare delivery organizations' experiences in integrating personalized medicine into clinical practice might further elucidate these challenges.

The analysis of common challenges presented in this report is largely qualitative and is limited to discussion among participants in the HWG. The collective perspectives of the HWG members may differ from those of representatives at other healthcare delivery organizations. The analysis in this report consisted of polling members, informal survey and consensus review, and did not account for differing perspectives within the HWG or measure the strength of agreement related to particular challenges. A survey targeting the broader healthcare delivery community and consisting of rankings of challenges might be able to provide quantitative analytics that could be used to better distinguish between differing perspectives of various types of healthcare delivery organizations.

Conclusion

As the healthcare system makes the transition from its traditional, one-size-fits-all approach toward a personalized medicine paradigm, it will be necessary to overcome challenges in several areas. Some strategies involving activities, programs and policies, such as those related to education and awareness and patient empowerment, can be implemented now or in the near term. Other strategies will require stakeholders to overcome reluctance to reshaping traditional practices and may require a cultural change in the way medicine is approached. However, progress made in addressing challenges in the areas where strategies are most straightforward and for which solutions are clearest should help increase our understanding of what is necessary to address more difficult challenges in other areas, thereby setting up a progression of solutions, ultimately fostering behavioral change that drives adoption of personalized medicine (Figure 1). For example, redesigning consent policies for the use of individual molecular data before problems arise and in a way that ensures patient privacy and data control could improve the process for collection and utilization of patient information for research and clinical care. Improved patient data processing would allow us

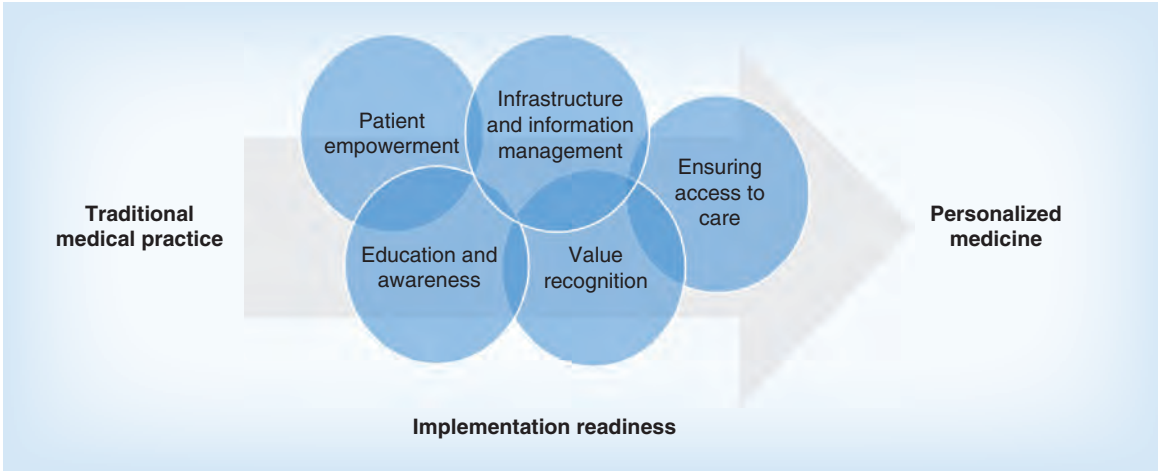

Figure 1. Progression of strategies by area of need for the transition from traditional medical practice to personalized medicine.

to devise more effective strategies for community-wide information management, which could, in turn, help reshape medical practice approaches and processes.

Paradigm shifts requiring cultural change typically happen slowly and often face resistance. However, when a new paradigm provides clear advantages, there is counter pressure to accelerate a shift in culture. In this context, we offer this report as a roadmap for the implementation of integration strategies to add more momentum toward effecting cultural change and a paradigm shift toward personalized medicine.

Future perspective

Currently, several healthcare delivery organizations are actively engaged in implementing personalized medicine programs. Understanding and communicating which policies and processes have worked best for these early adopters will help other organizations as they design and implement their own personalized medicine programs. This report highlights the need for a progression of strategic programs and efforts that encourage a paradigm shift. Implementation of these strategies uses a systems approach interfacing multiple disciplines including molecular biology, epidemiology and public health [39]. Basic strategic components to support personalized medicine could help foster system-wide directives and incentives that will be key to driving cultural change.

The initial stages of implementing personalized medicine programs will involve putting into practice strategies to address education and patient empowerment challenges while, at the same time, setting up appropriate leadership and forums to design and initiate programs and policies that will drive value recognition and effective infrastructure and information management. Implementing these strategies can position healthcare delivery organizations to address challenges related to adapting treatment approaches

Executive summary

Integration of personalized medicine

- Despite the steady increase in the number of clinically useful molecular diagnostics and targeted therapies, clinical adoption has been slow.
- Behind this lag in clinical adoption are novel challenges that healthcare delivery systems are encountering as they adapt to the new requirements, practices and standards associated with the field.

Education & awareness

- Healthcare providers, payers, employers and policymakers, as well as patients and their families, need to have a better understanding of personalized medicine concepts and technologies.

Patient empowerment

- Policies and practices related to patient engagement, privacy, data protections, and other ethical, legal, and societal issues regarding the use of individual molecular information must ensure appropriate consent and be acceptable to patients.

Value recognition

- Best practices must be established for the collection and dissemination of evidence needed to demonstrate clinical utility of personalized medicine and ensure the recognition of its value to care.

Infrastructure & information management

- Effective healthcare delivery infrastructure and data management systems need to be developed and applied so that individual patient and clinical support information is comprehensive, useful and user-friendly, and so that it can be used to guide clinical decisions.
- Processes for standardization of reported medical data, clinical support and outcomes information need to be developed so that information is exchangeable across multiple health IT platforms.

Access to care

- Best practices for healthcare delivery approaches, processes and program operations that ensure access to personalized medicine must be established and implemented.
- Practical strategies are needed to begin breaking down the cultural barriers to personalized medicine for the practitioner and the payer.

Roadmap for integration

- As the healthcare system makes the transition toward a personalized medicine paradigm, it will be necessary to overcome challenges in several areas.
- Some areas of challenges can be addressed through activities, programs and policies that can be implemented now or in the near term, while other areas will require a cultural change in the way medicine is approached.
- Progress made in addressing challenges in education and patient empowerment can help accelerate strategies to overcome challenges in other areas, such as value recognition and information management.
- As we increase our understanding of what is necessary to address more difficult challenges, there will likely be a progression of strategies, ultimately fostering behavioral change that drives adoption of personalized medicine.

and processes that will ensure access to personalized medicine and thereby continue to usher in a new era of medicine.

Supplementary data

To view the supplementary data that accompany this paper please visit the journal website at: www.futuremedicine.com/doi/full/10.2217/pme-2016-0064

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Strategies for delivering value from digital technology transformation

Eric D. Perakslis

Many organizations are attempting to harness emerging digital technologies and the surge in the amount of health-related data to drive advances in the development and use of medicines. Focusing on just a few well-proven and readily available strategies could enable such organizations to quickly realize greater value from data and digital technologies.

There is currently a lot of hype and hope about progress at the intersections of technology, health care and biomedical R&D, but transformational change and increased value still seem distant. Much has been promised around 'big data' and digital health, yet outdated IT infrastructure is a common challenge in many organizations. Striking new technology-enabled health-care capabilities, such as the first artifical pancreas (developed by Medtronic), are emerging, yet electronic medical records are now considered a leading cause of physician dissatisfaction. Real-world evidence on the use of medicines, molecular profiling of patients and data consortia are expected to drive improvements in biopharmaceutical R&D, yet examples are sparse. Here, I discuss proven strategies that could help organizations gain greater value from health-care data and digital technologies.

Turning innovation to transformation

Many organizations struggle to capitalize on potentially transformative technological innovation. In fact, innovation efforts are often physically and organizationally isolated from the operational aspects of an organization that they are best suited to help. The challenges include lack of ownership, outdated methodologies, outdated internal skills, lack of focus and concerns about upfront costs and long-term sustainability. The greatest opportunities lie in reconsidering the basics of how we evaluate, execute, support and exploit technological advances.

Changing approaches for technology evaluation. In biopharmaceutical R&D, the terms 'proof of concept' and 'proof of mechanism' are deeply ingrained, but analogous concepts are rarely used in technology evaluation. Pilot projects and prototypes are the most common approaches used when testing new technologies, but these often lack evaluation of existing technologies, a specific hypothesis, bias-free evaluation criteria and, most importantly, a clear understanding of interdependencies and mechanistic complexity. We must design technology experiments that are adequately powered to understand and transform the basics of operations.

Asking the right questions is also essential. Many organizations fail to understand that technology evaluation must involve assessment of their own capabilities, strengths and weaknesses, not just those of a potential partner. For example, when evaluating a technology that is already in use by peer organizations, the traditional vendor evaluation approach should be modified to include introspective study, particularly a focused evaluation of the underlying issues and complexity within one's own organization. Are the accessory technologies ready, do staff have the necessary skill sets and do they have the necessary sociological environment? In addition, external infrastructure can appear very expensive unless all fixed and sunk costs of internal infrastructure are truly accounted for. Lack of financial transparency across cost centres can obfuscate value assessments.

As an example, in 2010, the US federal government launched a 'cloud-first' initiative to decrease the footprint and expenses of federal data centres. A recent Government Accountability Office report (see Further information) shows that 3,125 of 10,584 data centres were closed by 24 federal agencies, with estimated cost savings and avoidance of US$2.8 billion for the fiscal years 2011–2015. This effort has also greatly improved the quality, availability and accountability of federal computing infrastructure. Interestingly, although security is often cited as the primary risk of cloud computing, 86% of the savings above were delivered from the US departments of Commerce, Defense, Homeland Security and the Treasury. Arguably, the national security and financial missions of these agencies show the new and necessary thinking that external infrastructure actually improves security when compared with internal capabilities.

Timeliness matters most. The most common failure in technology delivery is lack of timeliness. If precision medicine is about giving the right medication at the right dose to the right patient at the right time, then precision technology should be about organizations having access to the right technology when and where it is needed most.

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Once clear priorities are established, delivery depends on methodology and rapid execution. Traditional approaches to technology development are rigid and costly, especially if learning and adaptation along the way are expected. So, strategies to accelerate development are vital and we must be willing to diverge from traditional pathways. Agile technology delivery methodologies have been shown to minimize the waste inherent in redundant meetings, repetitive planning, excessive documentation, quality defects and low-value features, while simultaneously improving customer engagement, programme adaptability, quality and predictability[1]. Truly agile efforts deliver useful and usable value within 6 months, limit development phases to 3–6 months, simplify complex problems and increase participant satisfaction.

For example, using an agile approach to mobile app development, the Société Canadienne du Cancer deployed three versions of applications aimed at smoking cessation in millennials, each of which had evolved and included significant new functionality and features, based on input and use of the earlier versions. This was accomplished with fixed budgets and timelines, allowing them to transform a small-scale project into a full-scale programme with greatly enhanced functionality[2].

Listening (better) to patients. Patient-centric, patient-focused and patient-centred outcomes are now ubiquitous terms, but are we really listening to what patients want? What is most important when a complete cure is unavailable? A recent study examined the overlap of scientific literature topics on paediatric atopic dermatitis (AD) with 10,000 online posts from seven social network AD communities. After filtering for terminology and language differences, it was found that 70% of the topics discussed in those online communities did not appear in the published literature[3]. This gap is striking, both as a research opportunity for AD and also as an example that we must listen more closely and differently to patients to deliver truly patient-centric solutions.

There are no dirty data, just 'wild-type' data. A common criticism of real-world data and patient-reported outcomes is that the data are 'dirty' owing to the lack of structured language, such as that found in regulated clinical trials. When listening to patients, clinicians are taught to ask smart questions and be careful, cognizant of bias and critical but compassionate. Patients can be confused, embarrassed, biased and even dishonest during consultations. but clinicians must work with the data they receive. The data are not dirty; they are simply naturally occurring or wild type, and the highly constrained and overengineered contexts in which most clinical data are managed and studied are artificial. In fact, much key information is lost when we apply rigorous filters. The language processing technologies to use all forms of wild-type data and truly listen to patients exist and should be applied.

Most organizations have substantial amounts of unstructured and unaligned data coming from within, as well as from external sources. Traditional approaches to extracting value from such data have involved large, lengthy and expensive standardization, curation and data warehouse development. However, this may not always be necessary. For example, Mississippi is currently 50th out of 50 US states in health status, 50th in the number of physicians per 100,000 residents and not an advanced hub of silicon technologies. Nevertheless, the state successfully built and used a data lake to break down data silos and successfully connect multiple academic, medical and state health organizations to transform the field of health planning in Mississippi in a way that clearly saved significant amounts of time and money[4].

How are patients feeling 24:7? The use of wearable technologies and mobile apps for passive phenotyping, therapeutic and observational gamification and many other uses is exploding, and a few trends are emerging. Consent and compliance tend to be very high, especially in younger populations. Indeed, in two of Takeda's initial studies involving wearable technologies, consent rates of 70% and 80% were achieved. However, the consumer electronics market is focused on recreation, not medical research, so, for most biopharmaceutical applications, the most viable wearable technologies will originate from traditional medical device pathways. There is also a great variety of applications and each experiment is unique, requiring novel technologies. The development process for wearable technologies is therefore laborious.

Testing cyber security controls. Given the threat of cyber crime on health care, financial institutions and national security, cyber security must be managed as a core competency in technology delivery. Sound security is a competitive advantage and strategies must be tested. Just as mock audits are essential to understanding compliance status, thorough testing is the only way to assess the effectiveness of policies, technologies and controls.

Conclusion

Many of the tools and techniques needed for data and digital transformation are already available. We must evolve our basic strategies to harness the value for our organizations and for patients awaiting our successes.

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Competing interests statement
The author declares competing interests: see Web version for details.

FURTHER INFORMATION
Government Accountability Office Report to Congressional Committees. Data Center Consolidation. Agencies Making Progress, but Planned Savings Goals Need to Be Established. GAO-16-323: http://www.gao.gov/assets/680/675592.pdf

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RESEARCH ARTICLE

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

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Abstract

A new wave of portable biosensors allows frequent measurement of health-related physiology. We investigated the use of these devices to monitor human physiological changes during various activities and their role in managing health and diagnosing and analyzing disease. By recording over 250,000 daily measurements for up to 43 individuals, we found personalized circadian differences in physiological parameters, replicating previous physiological findings. Interestingly, we found striking changes in particular environments, such as airline flights (decreased peripheral capillary oxygen saturation [SpO_2] and increased radiation exposure). These events are associated with physiological macro-phenotypes such as fatigue, providing a strong association between reduced pressure/oxygen and fatigue on high-altitude flights. Importantly, we combined biosensor information with frequent medical measurements and made two important observations: First, wearable devices were useful in identification of early signs of Lyme disease and inflammatory responses; we used this information to develop a personalized, activity-based normalization framework to identify abnormal physiological signals from longitudinal data for facile disease detection. Second, wearables distinguish physiological differences between insulin-sensitive and -resistant individuals. Overall, these results indicate that portable biosensors provide useful information for monitoring personal activities and physiology and are likely to play an important role in managing health and enabling affordable health care access to groups traditionally limited by socioeconomic class or remote geography.

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Abbreviations: BMI, body mass index; BPM, beats per minute; COH, Change-of-Heart; HR, heart rate; hs-CRP, high-sensitivity C-reactive protein; IR, insulin resistance; IRB, Institutional Review Board; mRem, millirem; SD, standard deviation; SpO_2, peripheral capillary oxygen saturation; SSPG, steady-state plasma glucose; T2D, type 2 diabetes; WA, Welch Allyn.

Author Summary

A new wave of wearable sensors allows frequent and continuous measurements of body functions (physiology), including heart rate, skin temperature, blood oxygen levels, and physical activity. We investigated the ability of wearable sensors to follow physiological changes that occur over the course of a day, during illness and other activities. Data from these sensors revealed personalized differences in daily patterns of activities. Interestingly, we discovered striking changes in particular environments such as airline flights. Blood oxygen levels decreased during high-altitude flights, and this decrease was associated with fatigue. By combining sensor information with frequent medical measurements, we made two important health-related observations. First, wearable sensors were useful in identifying the onset of Lyme disease and inflammation. From this observation, we then developed a computational algorithm for personalized disease detection using such sensors. Second, we found that wearable sensors can reveal physiological differences between insulin-sensitive and insulin-resistant individuals, raising the possibility that these sensors could help detect risk for type 2 diabetes. Overall, these results indicate that the information provided by wearable sensors is physiologically meaningful and actionable. Wearable sensors are likely to play an important role in managing health.

Introduction

Physiological parameters such as heart rate (HR), blood pressure, and body temperature can provide critical information about the physical health status of a person. Elevation of any of these parameters can be of concern; elevated HR and blood pressure are associated with cardiovascular disease, and elevated body temperature occurs during pathogen infection and inflammation [1–4]. Peripheral capillary oxygen saturation (SpO_2) is a measure of oxygen saturation of hemoglobin in the blood, and patients with chronic pulmonary disease often have lower resting SpO_2 and are required to use supplementary oxygen to attain a more optimal SpO_2 [5]. Skin temperature is associated with alertness levels and quality of sleep [6,7]. Although these different parameters are routinely measured in the physician's office, they are not generally monitored outside of that context.

The infrequent collection of these measurements as currently practiced is problematic. First, changes in these parameters may not be identified until many months after an initial health condition has occurred. For instance, if a healthy person with reasonable health care access visits his or her physician every 2 y for a routine visit, then a condition may arise many months, or even longer, prior to a clinical symptom onset and thus go undetected for some time. Second, physiological parameters vary among individuals depending on their gender, life stage, and physical training, among other characteristics (e.g., [8,9]). These parameters also vary within the same person during their daily activities and with changes in the ambient environment. Because sparse clinical measurements of an individual are often compared to the average measurements of a population, the large variation within and among individuals results in a difficult medical assessment. Thus, infrequent short measurement periods or lack of adequate health care access makes it difficult to ascertain if a significant health change has occurred in a particular person. This information is particularly valuable for caregivers responsible for the health of others.

Emerging wearable biosensors (hereafter called "wearables") are a low-cost technology that either continuously or frequently measures physiological parameters and provides a promising approach to routinely monitor personalized physiological measurements and potentially

identify alterations in health conditions. Wearables are capable of passive and routine recording and immediate delivery of multiple types of measurements in real time to the wearer or physician with minimal attention or training required. In addition to physiological measurements such as HR and skin temperature, wearable technology has the potential to precisely capture the wearer's daily physical activities, such as walking, biking, running, and other activities, often in conjunction with a GPS, which provides direct information about the location of the activity.

The popularity of wearable devices has substantially increased in recent years. As of July 2015, there are more than 500 different health care-related wearables present on the market and over 34.3 million devices sold. This is triple the number sold in 2013 [10].

Despite the revolution of wearable technology, studies to investigate their use in health care have been limited. One recent study using biosensors found no obvious benefit to users in health care costs or utilization [11]. In this work, we investigate the use of portable devices to (1) easily and accurately record physiological measurements in individuals in real time (or at high frequency), (2) quantify daily patterns and reveal interesting physiological responses to different circadian cycles and environmental conditions, (3) identify personalized baseline norms and differences among individuals, (4) detect differences in health states among individuals (e.g., people with diabetes versus people without diabetes), and (5) detect inflammatory responses and assist in medical diagnosis at the early phase of disease development, thereby potentially impacting medical care. In addition to a number of novel observations, through these analyses, we have gained considerable insight into the capabilities and value of these different devices in health and scientific research.

Results

Overview of the Approach

Our strategy was to intensely study one individual with many devices in order to determine the ease of collecting different types of data and to identify interesting patterns and then extend our analyses to a cohort of participants using a more limited number of devices (Fig 1A). We began by routinely measuring a 58-y-old male (Participant #1) over the course of 24 mo (Institutional Review Board [IRB] protocols IRB-23602, IRB-34907). From an extensive list of candidate devices, we selected seven that were easy to use, had reasonable accuracy, and had a direct interface for raw data access (see Material and Methods). The list of devices and their measurements is presented in Fig 1. These devices collectively measure (a) three physiological parameters, including HR, SpO_2, and skin temperature, (b) six activity-related parameters, including sleep, steps, walking, biking, running, calories, and acceleration forces caused by movement, (c) weight, and (d) total gamma and X-ray radiation exposure. Collectively, these devices record more than 250,000 measurements each day (Fig 1). Many of the devices measure the same parameters, enabling cross-device comparison and assessment of measurement accuracy. During this period, Participant #1 also recorded the activities and travel in real time using web-based and smartphone-based software (see Material and Methods for details). Through numerous airline flights (S2A Table), an extensive analysis of the effects of air travel was assessed. Most information was collected through a smartphone, and all data were stored in a common database. Importantly, during the 2-y monitoring period, the participant was extensively monitored (73 visits) with standard medical tests, enabling a detailed comparison of medical data to the wearables information (S3 Table summarizes the medical tests performed in each examination).

In addition to a comprehensive analysis of a single individual, we also analyzed a larger group of participants to examine the consistency of our findings and explore differences and

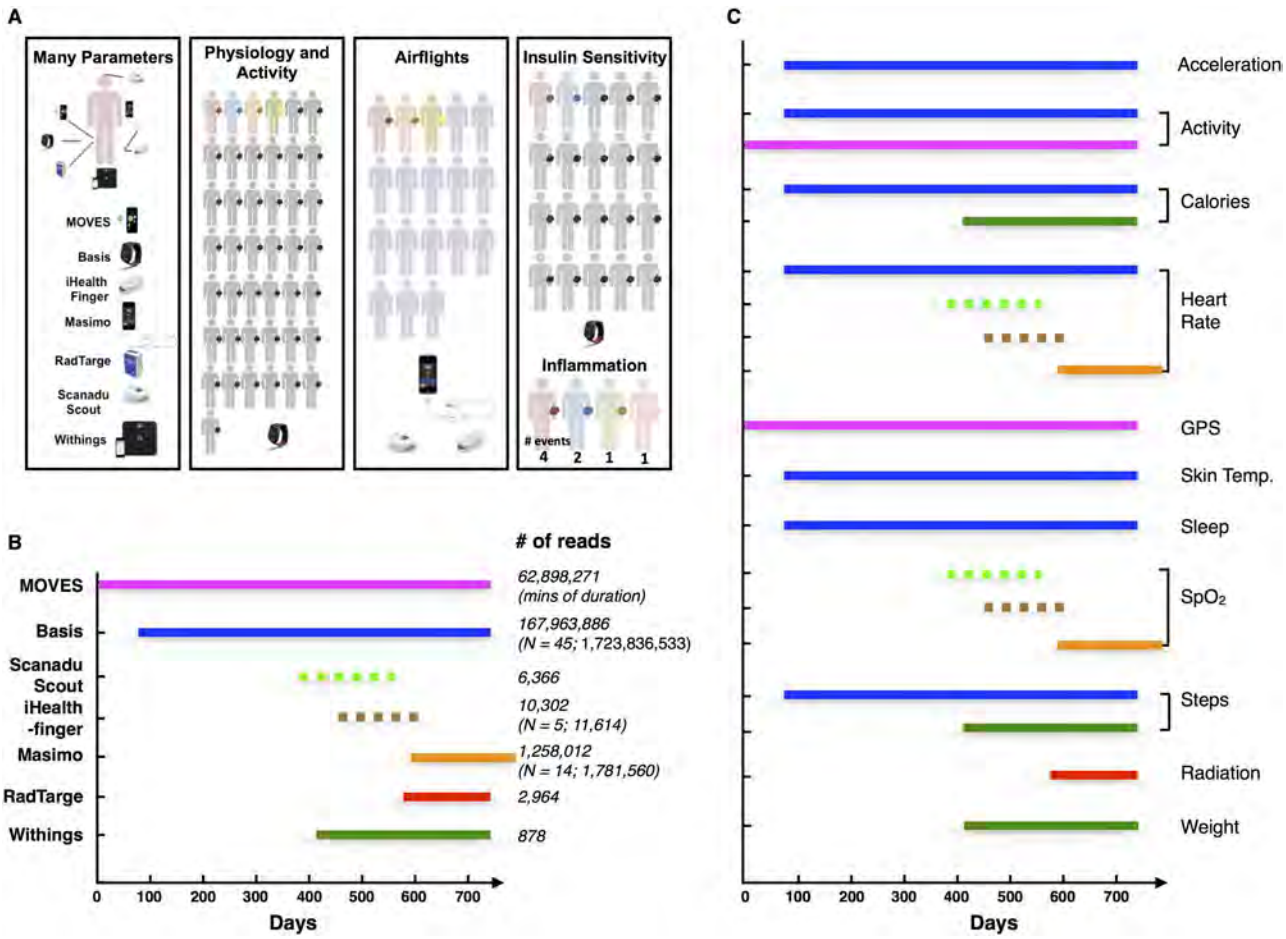

Fig 1. Overview of the project and summary of the devices. (A) Wearable devices used in this study. The different colors for the human figures indicate the specific studies in which each individual participated (i.e., red participated in all five studies, grey in two studies [Physiology/Activity and Insulin Sensitivity], blue in three studies [Physiology/Activity, Insulin Sensitivity, and Inflammation], orange and yellow in two studies [Physiology/Activity and Airflights], and green and pink in one study [Inflammation] and purple in one study [Airflights]). (B) The period during which the devices were used. The number of data points available for Participant #1 and others is indicated to the right. (C) The specific parameters measured by the different devices. The devices used to measure these parameters were represented by the color of the lines (MOVES: magenta; Basis: dark blue; Scanadu Scout: light green; iHealth-finger: brown; Masimo: orange; RadTarge: red; Withings: dark green). Dashed line indicates devices used frequently for discrete measurements; solid lines indicate devices that provide continuous measurement.

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similarities across individuals (Fig 1A; IRB-23602, IRB-34907). Eighteen participants (ages 28 to 72; IRB-34907, whose enrollment criteria were all individuals ages 13 and older were eligible, see Materials and Methods) were analyzed for the effects of airline flight on SpO_2 levels (IRB-34907; S1B Table). Our analysis of personal baseline and health also included physical monitoring of 43 individuals ages 35 to 70 y using a Basis device for up to 11 mo (average of 152 d; IRB-23602 and IRB-34907; individuals 18 or older were eligible, with a preference for those at risk for type 2 diabetes [T2D]; see Materials and Methods). The latter group is not T2D as defined by fasting plasma glucose <125 mg/dL and is free of chronic inflammatory conditions and major organ diseases. Four individuals, who self-reported as ill and had Basis Peak devices, were analyzed for the capacity of wearables to facilitate illness diagnosis and monitoring. Twenty individuals had quantification of systemic insulin resistance (IR) via the steady-state plasma glucose (SSPG) test as originally described and validated [12,13], and twelve of those

individuals were classified as insulin resistant (S1A Table; SSPG greater than 140 mg/dL [14,15]). All together, over 1,788,538,186 measurements from 7,234 d were recorded.

Summary and Validation of the Devices

Several of the devices, including the Basis device, used most frequently in our study had been validated for clinical-grade accuracy by the manufacturer (See Materials and Methods for details). Nonetheless, we performed extensive testing to assess the accuracy of the different devices against gold standard measurements and/or our instrument (Welch Allyn [WA] 6000 series), which is routinely used at the clinical laboratory services at Stanford University. We found that HR and SpO_2 data collected using four devices (Scanadu Scout, iHealth-finger, Masimo, and Basis) were very close to that of the WA instrument over a wide range of values using the Bland–Altman method of comparison [16,17] and the Pearson correlation test (see S1 Fig). For example, HR measurements were within five beats per minute (BPM) and 10% of the WA instrument for all devices. SpO_2 measurements were within 3% for all devices except for the Scanadu, which still yielded similar trends (see Material and Methods). Similarly we found that activity measurements were also close to standards for the conditions measured (e.g., MOVES App: steps: 0.79 +/- 0.16 standard deviation [SD] of the actual value; running: 0.96 +/- 0.05 SD of the actual value; details for all methods are presented in Material and Methods). Thus, we deemed the wearable biosensor measurements to be suitable for these studies.

Circadian and Diurnal Patterns in Physiological Parameters

In order to understand deviation from normal patterns, we first analyzed the collected data for systematic normal patterns, such as circadian rhythms, beginning with Participant #1. To reduce effects due to travel, our analyses focused on days lacking distance travel (defined as trips taken using airlines, assessed using GPS data from MOVES, and validated by comprehensive personal logs/calendars; see Material and Methods). Fig 2A–2D shows the circadian patterns of HR, skin temperature, and activity for 71 nontraveling d of Participant #1. As expected, we detected clear cyclical fluctuations over 24-h periods. For example, HR (measured using the Basis Peak) is generally lower at night (mean of 69.2 +/- 7.7 SD BPM from 10 P.M. to 6 A.M.) and higher during the day (mean of 84.5 +/- 11.3 SD BPM from 6 A.M. to 10 P.M.), with daily fluctuations (peak/trough or max/min) of 46.4 +/- 11.6 SD BPM (Fig 2B, S2A Fig), consistent with the sleep–wake cycle indicated by the Basis device (Fig 2A). Skin temperature measurements also generally followed a similar day-and-night pattern. Unlike that reported for core temperature [18], we found that skin temperature increases during sleep (a mean of 91.3 +/- 2.0˚F for 10 P.M. to 6 A.M.; a mean of 86.6 +/- 3.2˚F for 6 A.M. to 10 P.M., with daily fluctuations of 11.5 +/- 2.9 SD˚F on average; Fig 2C, S2B Fig).

Comparison of physiological data with physical activity information revealed obvious activity-related physiological responses during specific time windows. Participant #1 often has an elevated HR during the 7 A.M.-to-8 A.M. and 6 P.M.-to-7 P.M. time windows, which included the typical time for bike commuting on weekdays (confirmed with daily calendar and consistent with MOVES information). On weekends, elevated HR was often evident in the 4 P.M.-to-6 P.M. window (S2 Fig), which is consistent with running activity measured using both the Basis device and MOVES. Overall, the correspondence of patterns detected with known activities indicates that the wearable devices can readily capture physiological information.

Physiological Parameters Change Dynamically with Human Activity

We also directly compared the physiological response in relation to different daily activities using data from the Basis device and MOVES apps (see Material and Methods). As shown in

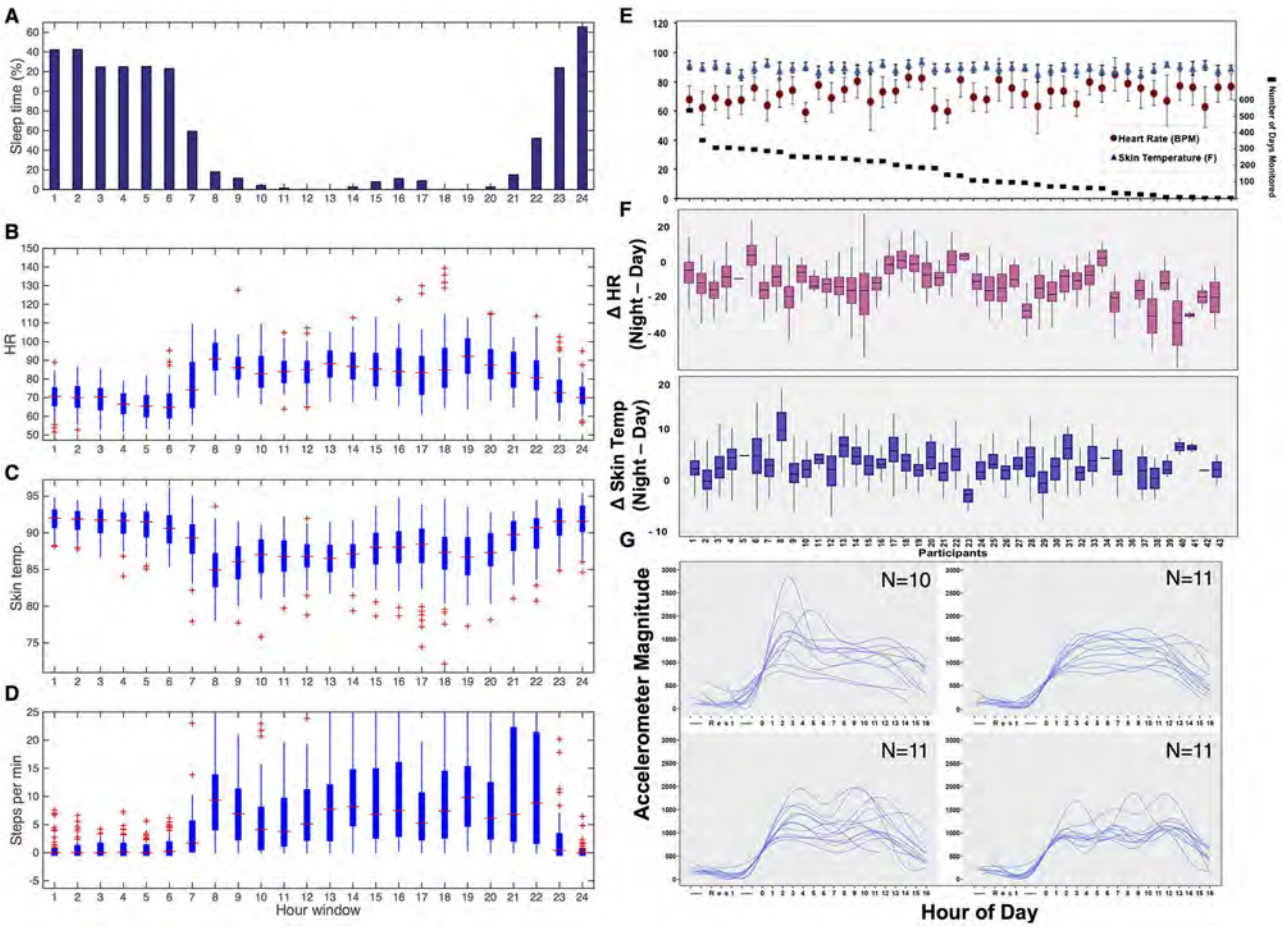

Fig 2. Circadian and diurnal patterns in physiological parameters. Participant #1 hourly summaries in (A) sleep, (B) HRs, (C) skin temperature, and (D) steps as measured using the Basis Peak device over 71 nontravel d. (E) Summaries of 43-person cohort for daily HR and skin temperature from all data and (F) differences in resting (fewer than five steps) nighttime and daytime HRs (Note: one person did not have nighttime measurements and is not included) and skin temperature. (G) Daily activity plots for 43 individuals. Based on number of peaks in the curves, four general patterns of activity behavior are evident. The plots in Fig 2G were aligned according to the first increase in activity.

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S3 Fig, our results replicate well-known patterns of physiological responses to events [19–22], including significantly faster HRs during exercise and significantly slower HRs during sleep compared to activity-free times, the mean of which is 78.4 ± 14.7 (SD) BPM; a mean of 67.6 ± 8.3 (SD) BPM, 101.1 ± 15.4 (SD) BPM, 114.1 ± 14.1 (SD) BPM, and 145.2 ± 18.1 (SD) BPM were observed during sleep, walking, cycling, and running, respectively (two-sided Wilcoxon rank sum $p < 10^{-32}$). As expected, the measurements of HR, steps, calories, and skin temperature are very consistent for most of the activities, except the step measurement during cycling, which is not accurately detected using the Basis device (S3 Fig). Importantly, as described below, examination of recorded notes revealed a significant decrease in SpO_2 levels measured by both the forehead and finger devices when Participant #1 reported fatigue (two-sided Wilcoxon rank-sum test $p < 0.05$; see below), and this finding was validated using systematic fatigue testing as described in the section on Airline Flights. Overall, these results indicate that our devices capture data as expected and also serve as a useful baseline to detect outlying measurements, as described below.

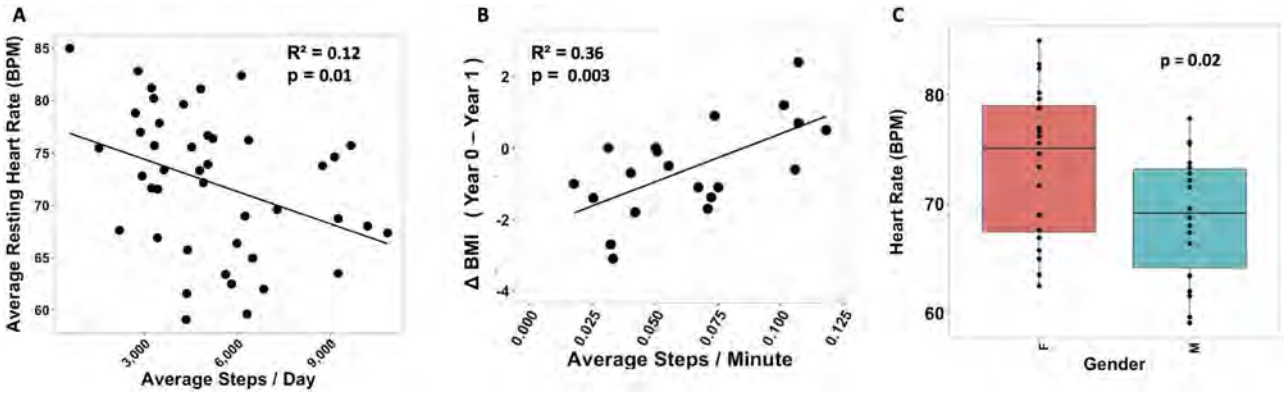

Fig 3. Physiological and activity profiles for 43 individuals. (A) The relationship between the average number of steps per day and resting HR (n = 43) and (B) average steps per minute and change in body mass index (BMI; n = 20) over the course of approximately 1 y was analyzed. Average resting HRs (C) were calculated by gender (see Material and Methods; n = 38).

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Personalized Physiological and Activity Profiles for 43 Individuals

We further examined physiological parameters and activity patterns for 43 participants, including Participant #1, who wore a Basis device for between 1 and 24 mo. For the overall cohort, the resting HR was 72.10 ± 6.75 (SD) BPM and the resting skin temperature was 89.19 ± 1.88 (SD)˚F. We found a significant difference in resting HR between men and women (Fig 3C): the resting HR of women was 73.70 BPM versus 68.80 BPM for men (p = 0.02248, Welch two-sample t test with 95% CI). These values are very similar to those reported by the NHANES study (74 BPM for women; 71 BPM for men) [23]. Women in our cohort also have a slightly higher average skin temperature (89.6˚F) than men (88.7˚F), but the value did not reach significance (p = 0.1724, Welch two-sample t test with 95% CI). In general, and as expected, we find that HR increases (S4A and S4B Fig) and skin temperature consistently decreases (S4C Fig) with increasing activity [21,22]. Furthermore, we see that the relationship between HR and skin temperature varies considerably among individuals (S4 Fig).

We analyzed the changes in HR and skin temperature between day and night for each of the 43 additional participants, although one individual (Participant #36) did not wear the Basis device while sleeping and was excluded from this analysis (Fig 2F). Average daytime HR (79.48 ± 6.96 BPM) was significantly higher than nighttime HR (66.99 ± 8.04 BPM; p = 4.836e-13, paired t test with 95% CI). The average difference between daytime and nighttime HR was 12.50 ± 7.80 BPM. Average daytime skin temperature (88.02 ± 2.02˚F) was significantly lower than nighttime skin temperature (91.49 ± 1.77˚F; p = 4.87e-13, paired t-test with 95% CI). The average difference between daytime and nighttime skin temperatures was 3.47 ± 2.17˚F. This is consistent with findings that skin temperature increases by 7.2˚F (winter) and 5.4˚F (summer) during sleep [24].

As shown in Fig 2E, the differences in resting HR and skin temperature values differ widely among individuals. For resting HR, the values vary from 59.09 ± 6.59 to 84.97 ± 11.29 BPM. The range of values for skin temperature is smaller than that of HR, with values of 84.44 ± 3.85 to 93.65 ± 2.05˚F, indicating tighter regulation of this physiological parameter. Although the Basis device has two sensors for detecting skin and ambient temperature, it is still possible that differences in skin temperature across individuals could be due to technical considerations in how the device is worn and/or exposed (S1C Table); however, the considerable differences in diurnal and nocturnal resting HR are likely to be due to personal differences between individuals because any measurement bias caused by how the device was worn is removed through

differencing of daytime and nighttime values. Overall, we did not detect an obvious correlation between HR and skin temperature; this might be due to complications from the diverse activities of the individuals.

We also examined the activity patterns of the 43 individuals using the Basis device data. The individuals fell into four major groups, including individuals with highest activity in the early morning (Morning Active; Fig 2G, upper left panel), sustained activity during the day (All Day Active; Fig 2G, upper right panel), or peaks in activity either two times (Commuter Active; Fig 2G, lower left panel) or three times (Mealtimes Active; Fig 2G, lower right panel) daily. The peaks for the latter two categories fall between mealtimes (i.e., mid-morning, mid-afternoon, and, for one group, in the evening). We used this finding to train functional clustering machine learning algorithms to classify individuals by activity group (S2 Fig).

Because increased activity is associated with overall fitness levels, we examined the relationship between activity, resting HR, and weight loss. We observed that a higher average number of steps per day is associated with lower resting HR (adjusted $R^2 = 0.12$, $p = 0.01462$; Fig 3A), and, when following changes over the course of 1 y, the increased average steps per minute is associated with a decrease in body mass index (BMI; adjusted $R^2 = 0.36$, $p = 0.003058$; Fig 3B). In general, individuals with overall higher activity levels have less of a change in HR between high and low activity periods (S4B Fig), indicating increased fitness levels. Overall, these result indicate that there are highly varied baseline physiological differences as well as activity differences among individuals that relate directly to clinically relevant parameters, suggesting that individuals have personal physiome and activity patterns that can be tracked using wearable sensors.

Significantly altered Physiology during Airline Flights

From our detailed analysis of Participant #1, a striking and interesting change in physiological measurements was observed during airline flights, and, consequently, we pursued an in-depth analysis of physiological parameters during air travel. Cabin pressure in an aircraft is normally maintained at a reduced level with a minimum value comparable to that of 8,000 feet altitude [25], although several modern aircraft have been advertised to maintain higher cabin pressure. For Participant #1, we measured SpO_2 and HR for 96 flights (summarized in S2A Table). The length of the flights varied from 23 min to 829 min, with 40 short flights (<2 h), 39 median-length flights (2–7 h), and 17 long flights (>7 h). Thirteen different aircraft models were included. The SpO_2 level of Participant #1 was monitored by a forehead device (Scanadu) and/or finger monitoring devices (iHealth-finger, Masimo) in a continuous (Masimo) or discontinuous manner (Scanadu, iHealth-finger). The FlightAware website (https://flightaware.com/) was used to track specific details about the plane routing, altitude, and speed for each flight in real time.

We observed a striking decrease in SpO_2 levels during airplane flights (a typical flight is shown in Fig 4A and S5A Fig), and this decrease is strongly negatively correlated with altitude. To summarize all flights, we binned each flight into five stages: before takeoff, ascent, cruise, descent, and after-landing stages (see Material and Methods). The overall distribution is shown in Fig 4B and S5B Fig for Scanadu and iHealth-finger measurements, respectively. Notably, Scanadu-measured SpO_2 levels were at 97%–100%, 91%–96%, and 90% or less for 31.2%, 54.0%, and 14.8% of measurements, respectively, in the cruising stage as compared to 64.1%, 31.7%, and 4.3% in the stage prior to takeoff and 73.1%, 24.0%, and 2.9% in the after-landing stage (Fig 4B); iHealth-finger-measured SpO_2 levels were at 97%–100%, 91%–96%, and 90% or less for 29.5%, 65.4%, and 5.1% measurements, respectively, in the cruising stage as compared to 88.0%, 10.8%, and 1.2% in the before takeoff stage and 80.6%, 13.9%, and 5.6%

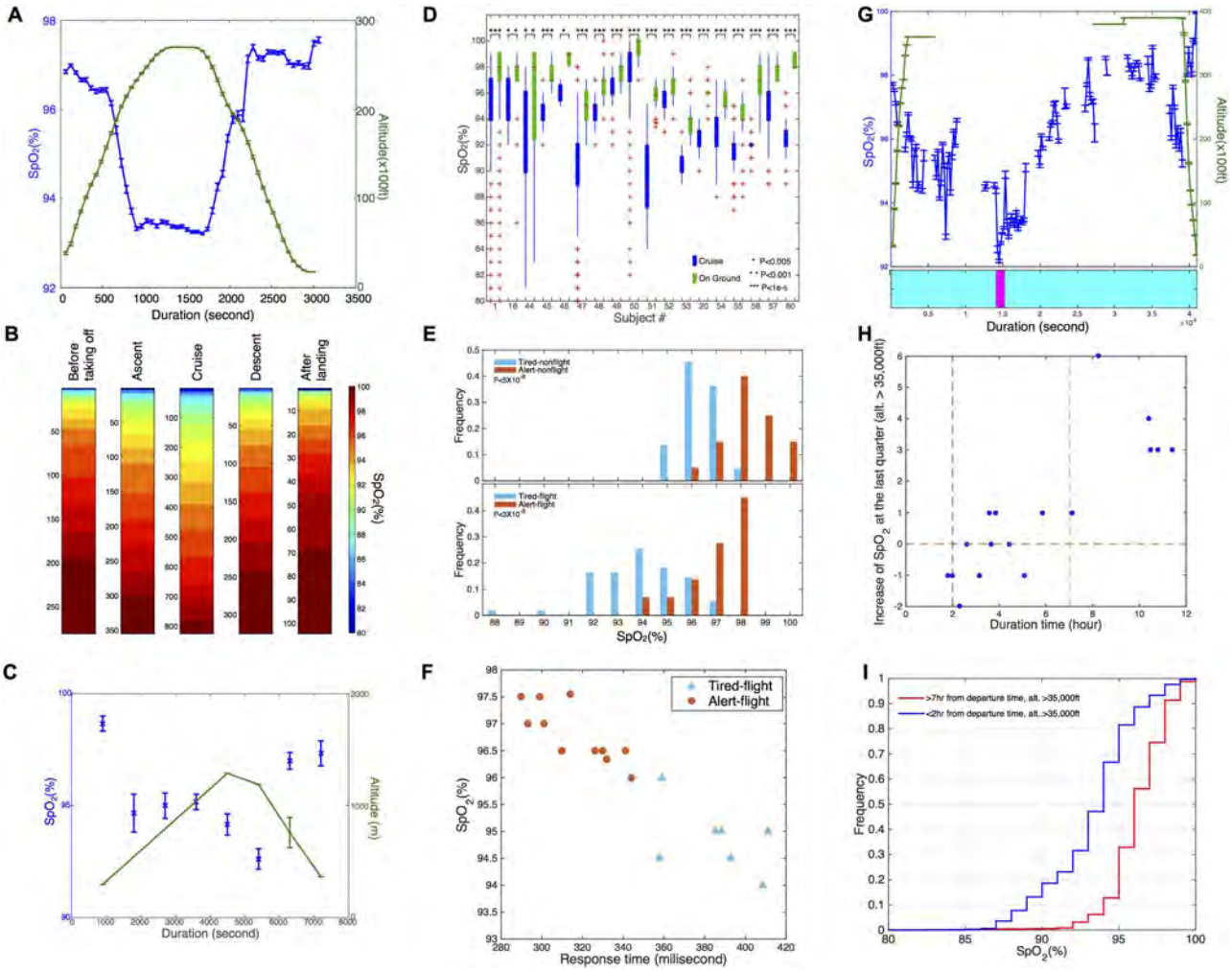

Fig 4. SpO_2 measurements during flight. (A) Example of a flight with continuous SpO_2 measurements (blue) taken using a Masimo finger device. Altitude recorded using FlightAware (green). (B) Heat map showing distribution of SpO_2 measurements recorded using a forehead Scanadu device at different flight stages: before takeoff, ascending, cruising, descending, and on ground post flight. (C) SpO_2 levels recorded using iHealth-finger device during 2-h automobile ride over a mountain. Average measurements and standard error measured over a 15-min window (Blue). Altitude recorded from sign markers or town elevations and/or using DraftLogic website. (D) Distribution of SpO_2 measurements taken from 18 individuals at cruising altitude (blue) versus on ground (green). (E) Distribution of SpO_2 measurements after the participant reported feeling alert (red) or tired (cyan). (Upper panel) Measurements from nonflying days. (Lower panel) Measurements from flying days. The significance of the difference between the two distributions was assessed by two-sample Kolmogorov±Smirnov test. (F) Scatterplot of response time and SpO_2 level recorded during one flight. The data recorded during another flight are shown in S5D Fig. The response time was derived from the psychomotor vigilance test to objectively quantify the fatigue of the participant. Self-reported tired and alert states are labeled by cyan triangles and red dots, respectively. (G) (Upper panel) Example of a flight with continuous SpO_2 measurements (blue) taken using a Masimo finger device. Altitude recorded using FlightAware (green). Note the increase in SpO_2 level towards the end of the flight. (Lower panel) Sleepiness recorded by Basis device. Magenta and cyan colors represent sleep and awake status, respectively. (H) A scatterplot of duration of time and the increase of SpO_2 in the last quarter. All data points were collected at altitudes higher than 35,000 feet. (I) Empirical cumulative distribution function plot of SpO_2 levels >7 h after takeoff (red) versus <2 h after takeoff (blue). All the data points were recorded at altitudes higher than 35,000 feet (p < 1e-307; two-sample Kolmogorov±Smirnov test).

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in the after-landing stage (S5B Fig). For the first 20 Masimo-measured flights, 19 had a significant inverse correlation of SpO_2 levels with altitude ($p < 4e\text{-}47$ for each flight; the remaining flight had technical issues, see Material and Methods for details; see also S6A and S6B Fig for an aggregate SpO_2 versus altitude of all flights, $p < 1e\text{-}307$). Thus, regardless of the device and flight, SpO_2 levels correlate inversely with altitude. Seating locations were not found to have an

effect on SpO_2 levels. Overall, we observed a drop to a SpO_2 of 96% or lower in all flights, and in many cases the drop was quite low (less than 94%) for a significant portion of the flight.

We hypothesized that the SpO_2 reduction is most likely due to the reduced air pressure, leading to reduced available oxygen at cabin altitudes. To evaluate whether the reduced pressure is the primary cause versus other flight-related factors, we also measured SpO_2 levels on a ~2 h automobile trip that climbed 993 meters and decreased 924 meters (altitude was determined by personal logs and the DraftLogic website https://www.daftlogic.com/sandbox-google-maps-find-altitude.htm; Fig 4C). SpO_2 levels tightly correlated with altitude, indicating a direct relationship between SpO_2 level and air pressure/oxygen [26].

Interestingly, we observed that on long flights the SpO_2 levels are higher toward the end of the flight than those at the beginning (a typical flight in shown in Fig 4G; data for a number of long flights are shown in S6 Fig). Among the 17 Masimo continuous recorded flights that have records for the last quarter of the flight, we observed that on long flights greater than 7 h, SpO_2 levels in the last quarter are significantly higher than at least one of the other three quarters measured at the same altitude level (Wilcoxon ranksum test $p < 1x10^{-29}$). and this observation was not detected on the short flights (Fig 4H). Furthermore, if we binned the Masimo-recorded, high-altitude (>35,000 feet) SpO_2 levels into two categories, (1) measured after 7 h from departure time and (2) measured earlier than 2 h from departure time, we observed significantly higher SpO_2 levels in the former category compared to the latter one. This increase is likely due to either adaptation or a physiological change after rest/inactivity. For the long westward flights, Basis-measured activity was relatively constant (i.e., primarily sitting >95% of the flight) and with little or no sleep (Basis-quantified and self-reported); an example is shown in Fig 4G, and the SpO_2 increase at the end of flight was always observed (see Fig 4G–4I and S6 Fig; Scanadu measurements are in S5F Fig), indicating that this increase is most likely due to adaptation. This observation demonstrates that humans can adapt to low oxygen after a number of hours on an aircraft.

To determine how SpO_2 measurements relate to macrophenotypes, we also examined physiological measurements during periods when the participant logged their alertness status as either "tired" or "alert" using a blind scoring system (its calibration has been quantified as described in Material and Methods). As shown in Fig 4E (bottom panel), the SpO_2 level reported when "tired" on flights was significantly lower compared to that measured when "alert" (two sample Kolmogorov–Smirnov test $p < 3x10^{-8}$), similar to that reported on nonflying days (Fig 4E upper panel, two-sample Kolmogorov–Smirnov test $p < 5x10^{-6}$). This observation was evident by both finger (Fig 4E) and forehead devices (S5C Fig). To be more quantitative in reporting fatigue, the participant also performed a psychomotor vigilance test and quantified fatigue by measuring the speed with which participants respond to a visual stimulus (see Methods and Material for details). As shown in Fig 4F and S5D Fig, a longer response time was required when the participant logged their state as "tired" rather than "alert," and the SpO_2 level is strongly negatively correlated with the response time (Pearson correlation test R = -0.88 to -0.91, $p < 6x10^{-5}$). This result not only validates the self-reported system of fatigue but also provides a quantitative summary of the relationship between fatigue and SpO_2 level. Although reductions in SpO_2 levels during flights have been reported previously [27–32], to our knowledge, this the first report of (a) adaptation on long flights and (b) fatigue levels on actual commercial aircraft with objective assessment of fatigue (see Discussion).

To further examine whether oxygen levels decreased in other individuals during airplane flights, we measured SpO_2 levels in 17 other individuals from diverse ethnic backgrounds (European, Jewish, African American, Indian Asian, and East Asian) using the iHealth-finger device or Masimo device (details in Material and Methods, S1B and S2B Tables). In every case,

decreased SpO_2 levels were observed during cruising (difference between median SpO_2 varies from 2% to 9%, two-sided Wilcoxon rank sum test $p < 0.001$). We also found that baseline SpO_2 and decrease in SpO_2 during cruising varies with different individuals (Fig 4D). A plot of altitude versus SpO_2 reveals that, in general, SpO_2 decreases are lower at lower-altitudes flights, and this is particularly evident for individuals with more than four flights (S6 Fig). Overall, these results indicate that reduced SpO_2 levels during air travel are a general phenomenon and occur in all types of aircraft. This result is consistent with published observations [27–32] and further indicates that the decreased SpO_2 during air travel is evident across different ethnic groups.

Diagnosis of Diseases Associated with Inflammation

To investigate the capacity of wearables to facilitate disease diagnosis and monitoring, we examined the association between unusual physiological signals and disease status or disease markers. This was uniquely possible for our study because we had frequently sampled and performed a number of biomedical assays during the entire monitoring period (see S3 Table for the list of tests).

We began our analysis by focusing on Participant #1, who was measured continuously for HR and skin temperature and frequently for SpO_2 levels for a period of 679 d (measurements were recorded for 603 d; see Material and Methods) and had a very large number of days (73) with extensive clinical testing during this period. As indicated above, physiological parameters change dynamically with daily activities (e.g., significantly faster HRs during exercise [S3 and S4A Figs] and significantly slower HRs during sleep [S3 Fig, Fig 2B and 2F]). Therefore, we compared each parameter according to the corresponding activity information (see Material and Methods for details) and chose those periods lacking physical activity to calculate the percentage-of-outliers (i.e., percentage of reads per day classified as outliers from the overall personal mean) to search for periods with significantly different measurements. During the 603 d of monitoring, we identified 8 d with abnormal HR and skin temperature pattern (Fig 5A; S7A Fig). Interestingly, most of these days fell into four periods that are of very high interest from a health perspective.

(1) The most significant period was a 5-d period (Days 470–474), during which we detected abnormally elevated HR (~14% to ~55% reads per day were defined as significant outliers compared to the corresponding baseline norm) and skin temperature (~5% to ~19% of the reads per day were defined as significant outliers compared to the corresponding baseline norm) during each of these days (Fig 5A and 5B). During this period, Participant #1 was suffering from Lyme disease (as diagnosed on Day 487 by a positive antibody test, S7D Fig). Lyme disease is a *Borrelia* bacterial infection primarily transmitted to humans through tick bites; 12 d prior to this period (on Day 458), the participant had been exposed to an area in rural Massachusetts where high levels of Lyme-infected ticks are present. (Note that a "bull's eye" rash was not observed during the initial period of infection). Importantly, the participant first noticed a possible health concern at the onset of the elevated HR/skin temperature period (on Day 470) and by abnormally low SpO_2 readings both during an airline flight and afterwards (Fig 5C). This elevated condition was followed over the next 4 d by a persistent elevated temperature reading with an oral thermometer (98.9–102˚F; see Material and Methods for details). Importantly, the normalized HR and skin temperature from the wearable device were significantly elevated multiple times during this period, and the HR exhibited a strong correlation with measurements taken with the oral thermometer over this period ($R = 0.81$, $p < 0.05$, S7B Fig). The participant visited a physician at Day 474 and received treatment with doxycycline; the symptoms and abnormal vital signs disappeared the following day (Fig 5B).

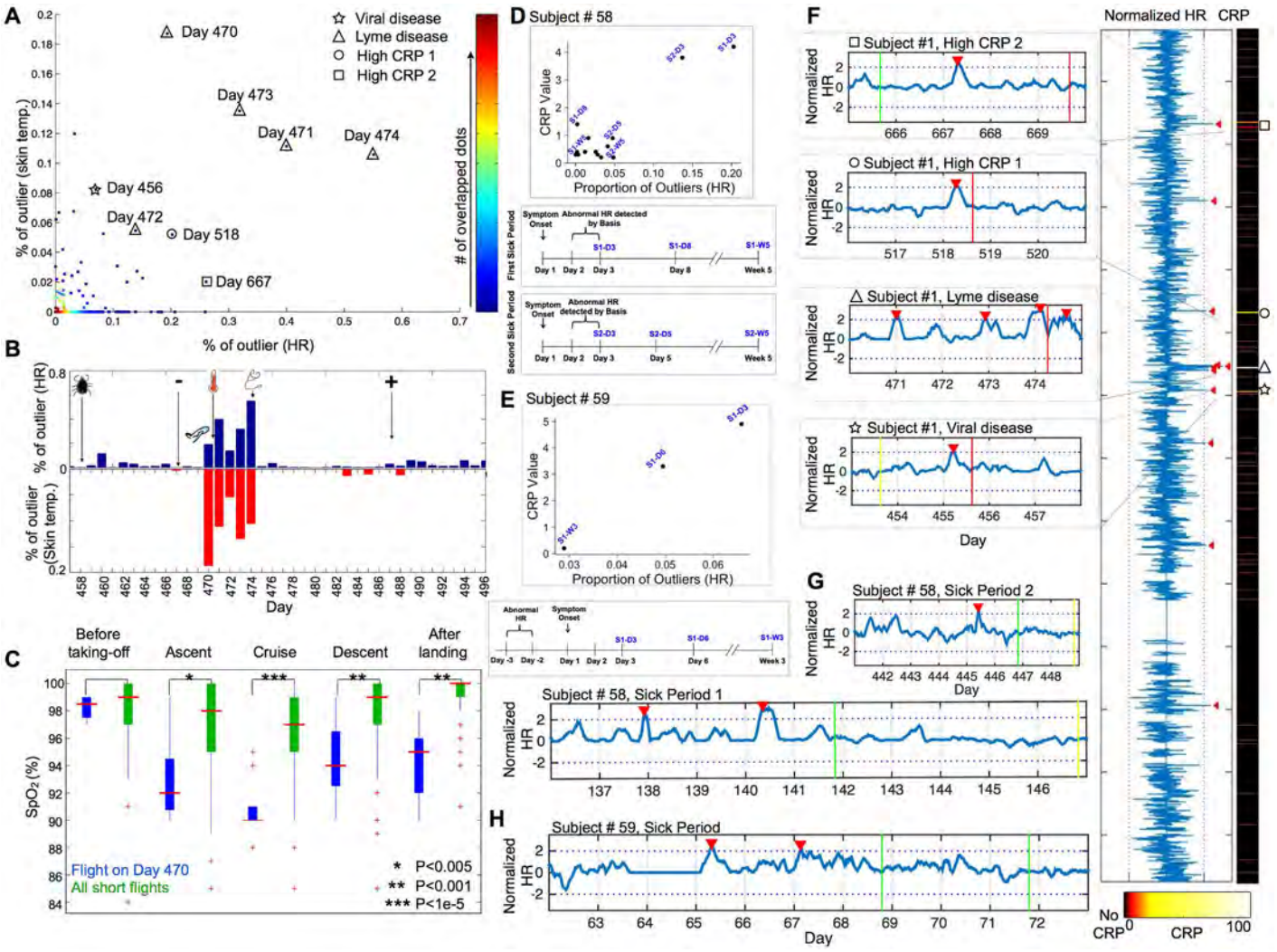

Fig 5. Elevated physiological measurements during infections. (A) Plot of fraction of outlying skin temperatures and HRs for all 679 d of Participant #1. Note all outlying time points correspond to periods when elevated high-sensitivity C-reactive protein (hs-CRP) measurements and/or illness were noted. The period harboring Lyme disease is expanded in panel B. (C) Decreased SpO_2 measurements during the flight and subsequent period when aberrant physiological measurements were first noted; boxplot shows SpO_2 distribution on Day 470 flight (blue) relative to similar length flights (green). The significance of this difference was assessed by two-sided Wilcoxon rank sum test. (D, E) CRP measurements are plotted against the proportion of daily HR measurements that were more than two SDs above the mean for Participant #58 (Pearson correlation coefficient = 0.90, p = 1.066e-05) (D) and Participant #59 (Pearson correlation coefficient = 0.966, p = 0.1653) (E). The timelines for the illness progression, CRP measurements, and Basis monitoring period captured in the figure are indicated for Participant #58 (two different illnesses separated by a period of ~11 mo) (Lower panel of D) and Participant #59 (Lower panel of E). (F) 679-d monitoring period of Participant #1. Left: normalized HR in minute resolution. Zoomed in at each illness period. Right: elevated CRP periods; G-H. Normalized HR at sick periods in minute resolution for Participant #58 (G) and Participant #59 (H). Red peak: Abnormal periods indicated by the peak caller. Red vertical line: CRP larger than 10; Green vertical line: CRP larger than three but smaller than ten. Yellow line: CRP smaller than three.

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(2) Another interesting period of outlying HR and skin temperature was Day 518 (Fig 5A, S7A Fig). About 20% of the HR reads and about 5% of the skin temperature reads on that day were defined as outliers compared to the corresponding baseline norm. Importantly, an elevated high-sensitivity C-reactive protein (hs-CRP) level was detected that day by a blood test (hs-CRP: 24.8 mg/L; baseline is normally <0.2 mg/L), although clinical symptoms (i.e., fever) were not reported. The elevated CRP, HR, and skin temperature were identified during data analysis.

(3) Another interesting period is from Day 455 to Day 456 (Fig 5A, S7A Fig). About 16% of the HR reads on Day 455 and about 8% of the skin temperature reads on Day 456 were classified as outlier compared to the corresponding baseline norm. Importantly, Participant #1 was diagnosed with a Human rhinovirus infection during this period (GeneMark test) and had elevated hs-CRP levels and inflammatory cell counts (hs-CRP: 16.2 mg/L, white blood cell: 10.8 K/ul, Neutrophil: 8.4 K/ul, 77.9%).

(4) Another interesting period is from Day 665 to Day 669 (Fig 5A). About 26% of the HR reads on Day 667 and about 2% of skin temperature reads were defined as outliers compared to the corresponding baseline norm. Importantly, an elevated hs-CRP level was detected on Days 665 and 669 by a blood test (hs-CRP: 4.3 mg/L and 15.4 mg/L on Days 665 and 669, respectively). The participant reported congestion during this period.

A plot of outlying HR and skin temperature as a function of time during each of these periods further demarcates their deviation from baseline and illustrates that the Lyme disease period has the highest outlying measurements (S8A Fig).

In summary, each of the circumstances with both elevated outlying HR and skin temperature was associated with elevated hs-CRP, indicative of a high inflammatory response (Fig 5A, S7 Fig), and for three of the four periods, clinical symptoms were reported. The participant did not report any other illness during this period of monitoring. These data indicate that there is a strong correlation between inflammatory response and elevated HR and skin temperature, which can be detected by wearables (Pearson correlation coefficient for CRP and the fraction-of-outlying-heart-rate (R = 0.96, $p < 10e\text{-}28$); coefficient for CRP and fraction-of-outlying-skin-temperatures (R = 0.94, $p < 10e\text{-}24$). For the case of Lyme disease, the abnormal physiological measurements of SpO_2 and HR were important in alerting the participant to the disease.

To determine whether disease-associated events might be detected in other individuals using wearables, we identified three other individuals in our cohort who self-reported as ill and had Basis devices (but not SpO_2 measurement devices; Fig 5D and 5E, S7E–S7G Fig). One individual had been ill twice. In each of these four instances, high CRP levels and elevated HRs were evident relative to their personal backgrounds (between 2.02 and 4.66 SDs above background). Although one of the individuals also had elevated skin temperature during this period (S7E Fig), interestingly, for two of the individuals (three illnesses), we did not detect elevated skin temperature. This might relate to differences in how the device was worn, as our survey results demonstrate that the device was worn loosely for at least one of these two individuals. As with Participant #1, for these three individuals, we also searched for other periods of elevated resting HR. For Participant #37, the illness period was the strongest outlier by a very large amount (4.66 SDs above background; rank #1 out of 25 d of monitoring for fraction of HR outlying measurements, S7F and S7G Fig). For Participant #58, the two illness days were in the top 5% of elevated HR outliers (3.40 and 2.02 SDs above background; ranks #10 and #19 out of 568 d of monitoring, Fig 5D), but we do not have the corresponding CRP levels to the other dates with outlying HR to know if those dates represent periods of illness/inflammation. For Participant #59, elevated HR occurred between 48–72 h prior to reported symptoms (3.55 SD above background; rank #1 out of 138 days of monitoring, Fig 5E) and elevated skin temperature on the day of and 48 h prior to reported symptoms (2.15 and 2.45 SDs above background, ranks #4 and #2 of 138 d of monitoring, respectively; S7E Fig).

In summary, we observed elevated HR during each ill period for all four individuals (eight total events), which suggests that monitoring of HR (and sometimes skin temperature) using a wearable device can detect inflammatory periods.

High-Resolution Mapping of Inflammatory Disease

To examine the resolution at which illness might be confidently identified, we developed a computational approach called "Change-of-Heart" or COH to identify periods with abnormal HR patterns. HR was chosen because, as described above, it reliably detected all periods with elevated CRP levels in each of the individuals. We were unable to reliably map elevated skin temperature at high resolution during these periods across all individuals, and thus this parameter was not pursued. Specifically, we focused on deviations in resting HRs relative to an inactive period and applied a peak-finding–based algorithm to the smoothed continuous HR signal to search for peaks different from a global and local distribution (see Material and Methods). This peak-finding method is optimal for identifying times of transition from healthy to ill states, and thus preferentially detects early periods of infection, which is most desirable.

As shown in Fig 5F, during the 679 d when Participant #1 was monitored, we identified 11 periods with elevated HR. These periods successfully tagged all of the four sick periods indicated above, sometimes with multiple peaks, and also revealed four other periods during which no illness was reported. Application of this approach to the other three individuals also revealed peaks during each of their ill periods. For all four individuals, we are able to identify all of the sick periods using this method with area under the receiver operating characteristic curves larger than 0.9 for each individual (S8B Fig). Importantly, each illness period is identified (100% sensitivity), and for most of the sick periods, significant signals were evident at the very beginning of the illness period. Overall, these results indicate that elevated HRs are present during illness and can be detected using wearable devices.

Physiological Differences in IR and Insulin Sensitivity are Detectable using Wearables

The availability of clinical measurements on our participants enabled us to investigate associations between information collected from wearables with clinically important data. We focused on diabetes-related measurements because many of our participants were at risk for T2D. Diabetes is a significant rising global health problem, and IR is highly correlated with progression to T2D [33]. Twenty individuals in our cohort underwent measurement of their SSPG, a direct measurement of resistance to insulin-mediated glucose uptake (See Material and Methods) [12,13].

We performed a stepwise modeling approach to examine the relationships between SSPG values and HR, activity, and BMI, beginning with a simple univariate model and then building to bi- and trivariate models. We first examined the associations between daytime, nighttime, and delta (daytime minus nighttime) HR and SSPG (Fig 6A, 6C and 6D) because of evidence that diabetes is associated with changes in diurnal variation of HR [34]. Both daytime HR (Fig 6C) and delta HR (Fig 6A) were positively correlated with SSPG (Daytime HR: $\beta = 4.5$, 95% CI 1.2–7.8), $p = 0.0107$; Delta HR: $\beta = 4.1$ (95% CI 1.1–7.1), $p = 0.0098$), but nighttime HR (Fig 6D) was not.

Because our previous results showed a relationship between overall activity and resting HR (Fig 3), we wanted to evaluate whether the relationship we discovered between daytime or delta HR and SSPG was due to differences in study participant activity. We first assessed whether there was a relationship between daily activity and SSPG (Fig 6B) and found that average daily steps had an inverse relationship ($\beta = -0.012$, 95% CI -0.022–-0.002, $p = 0.0183$) with SSPG. We also evaluated the relationship between average daily steps and HR and found that daily steps was not significantly associated with daytime HR ($\beta = -0.0008$, 95% CI -0.0021–0.0005, $p = 0.1943$) but did have a significant inverse relationship with nighttime HR ($\beta = -0.0017$, 95% CI -0.0030–-0.0004, $p = 0.0115$). Thus, the association of higher daytime HR with higher SSPG

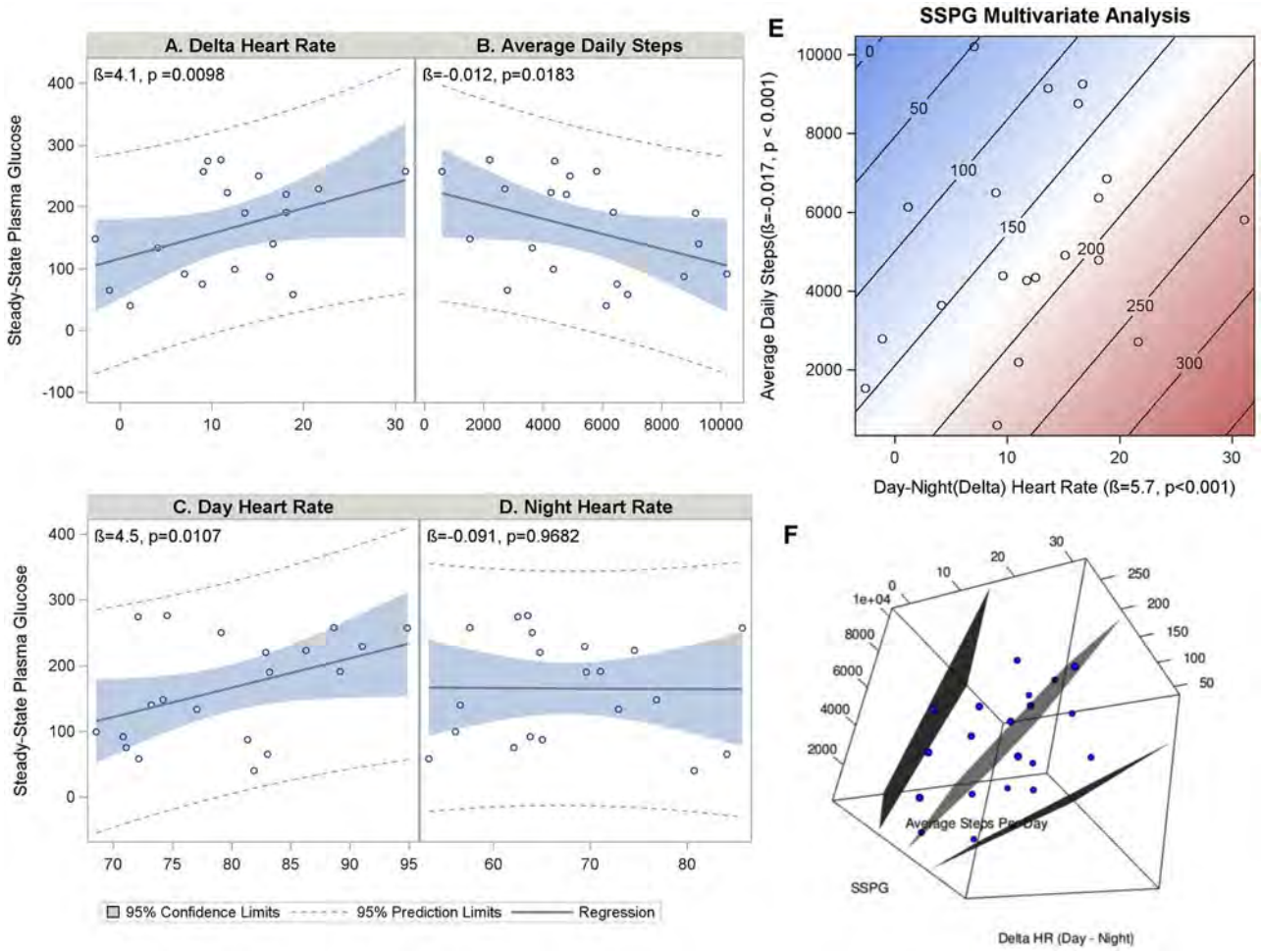

Fig 6. HR differences in IR and sensitivity. Fit plots (A±D) of the linear regression models showing the associations between daytime (C), nighttime (D), delta (daytime minus nighttime) HR (A), and average daily steps (B) with SSPG levels. Higher SSPG levels indicate increased IR. An increase in delta HR and daytime HR is associated with a higher SSPG level, whereas an increase in average number of steps taken a day is associated with a lower SSPG level. There was no association with nighttime HR. Contour fit plot (E) and 3-D plot (F) of the multivariate regression demonstrating that delta HR and average daily steps each have an independent inverse association with SSPG. Parameter estimates were obtained using restricted maximum likelihood estimation with a robust variance estimator to account for unequal variances.

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levels is unlikely to be due to differences in participant daily activity. Including overall activity in a multivariate regression model with delta HR to predict SSPG resulted in an improved adjusted R^2 to 0.41 from 0.17 in the univariate model with delta HR as the only predictor. These results suggest that information from different wearable sensor data types in combination can improve the ability to detect important physiological changes as compared to information from a single sensor.

To assess whether BMI plays a role in the relationship between delta HR and SSPG, we further expanded our multivariate regression to include BMI. BMI is known to have a positive correlation with HR [35], and IR and is negatively correlated with overall activity levels (Kruger et al., 2016). In this model, delta HR remained a strong predictor of SSPG levels (β = 5.05, 95% CI 2.73–7.37, $p = 0.0003$) independent of daily activity (β = -0.010, 95% CI -0.021–0.000, $p = 0.0509$) and BMI (β = 7.58, 95% CI 1.83–13.33, $p = 0.0130$, adjusted $R^2 = 0.52$). Thus,

combining information from multiple wearable sensors and electronic medical records to capture the relevant underlying physiological parameters enables enhanced prediction of SSPG. Overall, these results indicate that individuals with different degrees of IR and insulin sensitivity have important physiological differences and that these differences can be measured using wearable devices.

Exposure to Radiation

Lastly, to examine the diversity of measurements that can be quantified, we also explored whether individuals encounter periods of radiation exposure using a personal radiation tracker (RadTarge II D700) to monitor the local environmental radiation level over a 6-mo period. Fig 7 displays the distribution of radiation exposure over a 25-d period. As suggested by these data, Participant #1 typically lives in an environment with a low background radiation level around 0.003+/-0.0006 millirem (mRem) per h; however, several exposures of elevated radiation levels occurred. The majority (>90%) of the events over 0.030 mRem per h occurred during airplane flights, consistent with the expectation of increased exposure to cosmic radiation at high altitudes [36–38]. As shown in the enlarged panel, the radiation level per h generally corresponds closely with the interval and altitude of the airplane flight (typically rising to 0.038 +/-0.004 mRem/h for a 35,000–39,000 feet altitude flight), an increase of 12.7-fold over home

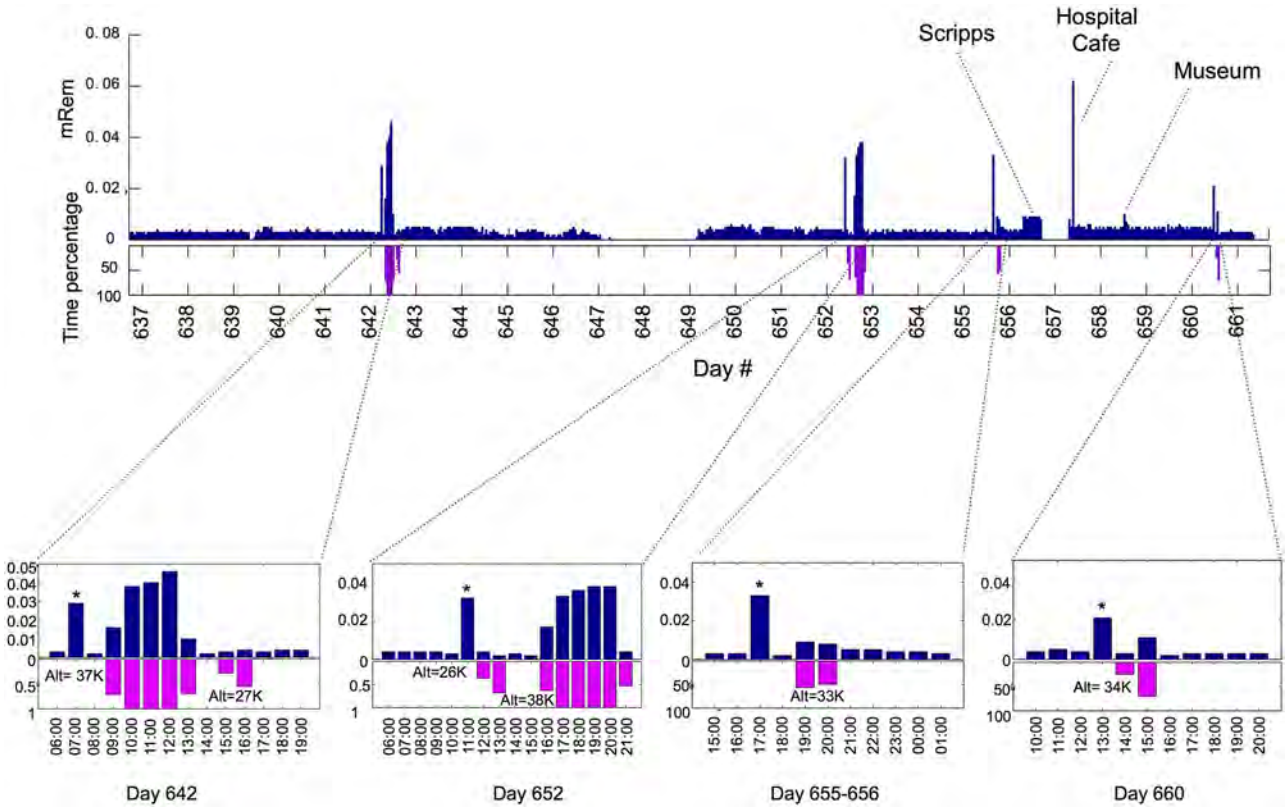

Fig 7. Exposure to radiation in daily life. Bar plot (upper panel: bars in blue) showing the amount of radiation that Participant #1 exposed to over a 25-d time window. Bar plot (lower panel: bars in magenta) showing the time that Participant #1 spent in airplane flights over the same time period. The maximum cruising altitude of each flight was labeled in the zoomed view of the bar plots. Asterisk represents the amount of radiation monitored during the airport carry-on luggage check (range 0.027 to 0.031 mRem). Other events that resulted in relatively high radiation are also labeled in the figure.

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background levels). Short flights with lower cruising altitude (a flight on Day 642 with a maximum cruising altitude of 27,000 feet and the one on Day 652 with a maximum cruising altitude of 26,000 feet) yield only modest increases in radiation exposure over the background. The increased exposure at high altitudes is consistent with the well-known fact that a radiation-protective layer of atmosphere surrounds the Earth and is diminished at higher altitudes [39].

Several other interesting periods of increased radiation levels were evident. A very modest increase was evident for an entire 8-h period at the Scripps Research Institute (3-fold) and in an underground museum in Los Angeles (also 3-fold). A very substantial increase (400-fold at peak levels) in higher radiation was detected when the participant entered a hospital café. This increased exposure lasted the entire 10–15-min period in the café but was not evident upon return to the same location two times later in the same day. A likely explanation for this observation is that the radiation source was present on someone in the café, most likely an individual undergoing internal radiation therapy. We did not detect differences in HR or skin temperature during this period. Overall, these data show that very modest increases in radiation are present in several locations in the country with more substantial increases during airline flights or during chance encounters with individuals or locations with high radiation. Most importantly, it demonstrates that simple personal wearable devices can identify these levels and provide immediate feedback.

Discussion

The data presented above indicate that many types of continuous physiological and activity information can be collected on a single individual on a long-term basis and can be used to measure, analyze, and guide health-related decisions. We showed that wearables can capture expected observations such as circadian fluctuation in HR and skin temperature and their changes during activity. In addition to serving as a valuable resource, we also found several interesting and important new results.

First, we found a decrease in SpO_2 levels on airplane flights, including the frequent intervals (14.8%) with very low SpO_2, with an adaptation toward more normal levels on long (>7 h) flights. The former has been reported previously [27–32], but, to our knowledge, the SpO_2 decrease on modern aircraft (including Boeing 787) and the interesting discovery of SpO_2 adaptation after approximately 7 h on long flights have not been reported. The SpO_2 decrease is unlikely to be due to inactivity because similar periods of inactivity not on flights did not associate with SpO_2 decrease. We suggest that the adaptation is due to altered physiology; it is unclear if frequent flying contributes to the adaptation response.

We also found a significant association of SpO_2 decrease with fatigue on airline flights, which replicates findings from experiments performed in controlled laboratory conditions [40,41]. However, laboratory conditions are not a perfect replication of actual in-flight conditions, and it is important to document these changes in actual flights and in modern aircraft. This is particularly important given that the large number (approximately 2.75 billion passengers fly on commercial airlines worldwide annually [42]) and the average age of air travelers has risen and many more people with chronic diseases fly. Wearables combined with subjective and objective measures open the possibility to study a much broader range of people under real-time flight conditions and provide monitoring of the effects of reduced air pressure on individual symptoms.

Second, we found a strong association between high HR and skin temperature measurements and elevated hs-CRP levels, consistent with previous studies using nonportable devices [43]. For the 603 d of Participant #1 monitoring, elevated hs-CRP, HR, and skin temperature were evident during four periods. Interestingly, for at least one of these periods (Day 518) the

participant was clinically asymptomatic, indicating that the inflammatory events were detectable by both a medical hs-CRP test and wearable devices, but not by the participant. Outside of these four periods, at low resolution, we did not detect any days with elevated hs-CRP that did not have elevated HR or skin temperature. Our high-resolution method using only HR also identifies the ill periods as well as four additional peaks and identifies the initial onset of disease for three of the four periods. For three other individuals an elevated HR was detectable during periods of high hs-CRP and illness, and skin temperature was elevated for one individual. In each case, the COH method identified an early stage of the disease. We suggest that wearable devices may be a sensitive measure for detecting certain inflammatory responses, and that in some circumstances, these may even be better than participant-reported observations.

It is possible that the use of wearables will lead to false alarms and overdiagnosis of disease. The number of false alarms will depend upon the threshold that is set, which can be personalized. It is notable that the most severe infection in this study, Lyme disease, which required physician intervention, had strong and repeated COH signals and is readily detected. Overall, we envision that these devices could be particularly powerful for individuals who are responsible for the health of others (i.e., parents and caregivers), and perhaps also for those who have historically limited health care access, including groups with low income and/or remote geography.

Of particular note was the detection of elevated skin temperature and HR as well as the decrease in SpO_2 at the onset of symptoms of Lyme disease. This information was quite valuable in early diagnosis and treatment and occurred in an instance in which the characteristic "bull's eye" rash was not observed after initial infection. Indeed, the symptoms first appeared after entry into a country in which Lyme disease was infrequent and the physician's initial recommendation of penicillin may have been an inadequate treatment. Moreover, the detection by wearables was quite robust, as outlying HR and skin temperature measurements were evident at every day of the disease. It is expected that the use of wearables for disease detection is extensible to other individuals and diseases associated with inflammation; obviously, the more serious the disease and associated inflammation, the more likely it will be detected using the portable devices. Indeed, the devices could be set to identify periods of highest inflammation (i.e., the ones that might require physician intervention) in order to reduce false alarms or avoid minor illness not requiring medical intervention.

Elevated HR is a strong predictor of cardiovascular disease and metabolic syndrome and is also associated with IR, insulin precursor presence, and the acute insulin response [44–48]. Hyperinsulinemia can trigger an increase in sympathetic activity through peripheral and central mechanisms [49–51]. Although the feedback loops are complex, this increase in sympathetic activity may contribute to the pathophysiology of IR, hypertension, and cardiovascular disease [52]. Our findings are notable in that we found a strong positive association between the difference of daytime and nighttime HR and participant SSPG levels that was independent of the effect of activity and BMI. This may indicate increased sympathetic activity reflective of complex physiological changes that are associated with IR and progression to diabetes. The fact that these differences can be measured using wearable devices raises the likelihood that this approach may someday be a useful measure for early detection of IR and risk for T2D.

Although many of the observations were originally discovered on a single person (who was also an author in this study—a potential limitation), in all cases, the results were validated on a larger cohort, demonstrating that our results can be generally applied. We also note that although up to seven devices were used simultaneously by a single person in this study, in addition to a scale to measure weight, in principle, all of the parameters measured in this study can be readily captured using two devices, a smartphone and a smartwatch, thus facilitating

data collection and integration of diverse data types. Finally, we note that many more analyses of these data can be carried out, some of which are best performed using data collected from individuals operating in a more controlled setting.

In conclusion, this study demonstrates that a diverse array of measurements can be systematically obtained using portable devices and used to monitor health-related physiology and activities. These measurements are likely to be important not only in basic science research but also in a clinical setting. It is likely in the future that these devices will be used by physicians to help assess health states and guide recommendations and treatments [53,54].

Materials and Methods

Human Cohorts and Ethics Statement

The participants were enrolled in this study under the IRB protocols IRB-23602 and IRB-34907 at Stanford University; the IRB approved the study and consent forms that were used. All participants consented in writing. All clinical measurements were covered by IRB-23602, the enrollment criteria of which was 18 y of age or older. All the wearable measurements were covered by IRB-34907, with the enrollment criteria as age 13 or older. The 43 activity participants were recruited with efforts to enroll those at risk for T2D (SSPG >140 mg/dL; fasting plasma glucose >100 mg/dL, Oral Glucose Tolerance Test >140 mg/dL, Hemoglobin A1C >5.6%) along with healthy controls. Other than IR and/or moderate hyperglycemia, all participants enrolled in this study are self-reported healthy. Age, sex, and ethnicity information was available for all SpO_2 participants and 38 of 43 Basis device participants and is indicated in S1 Table.

Selection of Wearable Devices and Data Acquisition

After evaluating more than 400 available wearable devices at the beginning of the study, we selected several for participants to use. The criteria for selection was (1) ability to access the raw data from the manufacturer, (2) cost, (3) overlap in measurement of at least one component with another device to assist in reproducibility, and (4) ease of use. Participant #1 wore seven portable devices for large segments of this study (Fig 1B); the remainder used a Basis device. For the SpO_2 measurements, three devices (Scanadu, iHealth-finger, Masimo) were used by Participant #1; either iHealth-finger or Masimo were used by the other participants.

For the Basis data, the manufacturer securely uploaded the data to a secured cloud storage system. For other devices, the data were collected by the user's smart phone, where the user securely transmitted the data to our repositories.

Data Description (Devices/Apps)

Each manufacturer and device outputs data in a unique, device-specific format. There are currently no standards and/or best practice recommendations on how the data should be recorded. Below are the data and metrics that were stored.

- Date/Time—all data points were recorded in different formats and annotated to note the time zone of the recording. (MM/DD/YYYY h:min:s -UTC)
- HR—(Basis B1, Basis Peak, Scanadu): BPM
- Accelerometer—(Basis B1, Basis Peak): data are derived on the device as the square root of triaxial acceleration: sqrt(x^2+y^2+z^2)
- Steps—(Basis B1 and Basis Peak, MOVES: algorithmically derived by manufacturer

- Activity—(Basis B1 and Basis Peak, MOVES): categories are algorithmically derived by manufacturer: running, walking, biking, transport (MOVES)
- Skin Temperature—(Basis B1 and Basis Peak), degrees Fahrenheit
- Calories—(Basis B1 and Basis Peak): algorithmically derived by manufacturer

Additional parameters (galvanic skin response, food logging, and continuous glucose metrics) were also collected and will be the subject of another study.

For Participant #1, over 250,000 measurements were recorded daily using a combination of the MOVES App, the Basis device, and other wearables.

Assessment of the Validity of the Wearables Measurements

Many of the devices have been validated for accuracy by the manufacturer (e.g., Basis: https://258b1w36g2mmq40rp2i2rutg-wpengine.netdna-ssl.com/wp-content/uploads/2015/12/12212015_UCSF_WhitePages.pdf; http://www.mybasis.com/wp-content/uploads/2014/04/Validation-of-Basis-Science-Advanced-Sleep-Analysis.pdf). Nonetheless, we compared the SpO_2 and HR measurements from the Masimo, Scanadu, iHealth-finger and Basis devices to those from our standard WA 6000 series vital signs monitor used in the clinical service laboratory at Stanford University. Measurements were taken at three or more different days. Finger measurements were made on either the right index finger or right ring (fourth proximal) finger; no detectable differences (<1%) were found when compared to the WA instrument using simultaneous measurements of the WA and wearable device, i.e., simultaneous tests were run on the wearable and WA device; as controls, finger locations were also swapped for the two devices and the WA instrument). To cover a wide range of SpO_2 levels and HRs, the participant held his breath and the measurements were made simultaneously (within 2 s) on two different locations using one device and the standard instrument. For finger-based measurements, similar numbers of measurements were made switching the device locations. The comparison across devices was done by matching the time stamps. The Bland–Altman method [16,17] and Pearson correlation were applied to assess the agreement and the relationship between the wearables and the clinic devices, respectively. As shown in S1 Fig, for SpO_2, 100% of the Masimo and iHealth-finger and 85% of the Scanadu measurements were within three percentage points of the WA instrument. For HR, over 95% of all portable device measurements were within three BPM of the clinical equipment (100%, 97.1%, 97.5%, and 93.5% for the Scanadu, iHealth-finger, Masimo, and Basis, respectively.) Although this percentage was slightly lower for the Basis, 100% of the Basis measurements were within the accuracy criteria of the Association for the Advancement of Medical Instrumentation for HR meters (five BPM and ±10% of the WA instrument) [55]. There was no evidence of systematic bias in the measurements (S1A–S1D Fig) with the exception of the Scanadu SpO_2 measurements, in which the majority of readings were slightly higher than the clinical device and a few were much lower (S1C Fig); in all HR cases, the averages were within one BPM of the mean.

Pearson correlation analyses also revealed tight correlation of the wearables measurements with standard medical devices (R = 0.77 to 0.96, $p < 0.0005$; S1 Fig). The only exception was the Scanadu SpO_2 measurements (R = 0.46). The Scanadu measures HR and SpO_2 from the forehead, whereas all the other devices including the standard medical device record measurements from the finger. It is not clear whether our findings are due to technical differences of the device or the location of measurement [56]. Regardless, as described below, the trends for SpO_2 levels (and other parameters) under different conditions are identical among each of the different devices.

In addition to the physiological measurements, we also assessed the accuracy of the activity data. First, we examined the agreement and correlation between the activity-sensing devices (Basis, MOVES, Withings) (See S1 Fig). The Pearson correlations between devices ranged from 0.74 to 0.81 (all p-values <0.00001; S1 Fig). The Bland–Altman Plots revealed that at daily step counts less than 12,000 steps, there was good agreement between the Basis and Withings devices. However, as daily step counts increased above 15,000 steps, the Basis gave higher step counts than the Withings device. Both Basis and Withings devices gave higher measurements than the MOVES device. The MOVES step measurement was compared using absolute measurements. Specifically, we manually counted 100 steps 12 separate times at three different locations (Bay area, Geneva, Uppsala) and compared the MOVES-recorded steps with the actual steps. The values recorded were found to be 0.79 +/- 0.16 SD of the actual value. To measure running distances, we compared two runs over a measured distance of 3.2 miles; the measured values were 0.94 +/- 0.04 that of the actual value. We also performed similar comparisons at different geographical locations by analyzing 13 outdoor runs at three different locations and compared the distances with those derived from Google Maps (for two locations, distance was confirmed using an automotive odometer). The values recorded were found to be 0.96 +/- 0.05 SD to that measured using Google Maps. Comparison of MOVES results with those of three runs using treadmills showed a larger difference of 0.75 +/- 0.22 SD.

To assess the agreement of measurements of steps using the Basis Peak device and MOVES and Withings applications, we compared the total number of steps per day for the 132 "nontravel days." Time zone conversion was applied to make the three devices comparable. The Bland–Altman method and Pearson correlation were applied to assess the agreement and the relationship between the devices (S1 Fig).

We note that the devices were assessed under a limited set of conditions and that not all possible conditions were assessed.

Analysis of Circadian and Diurnal Rhythms in Physiological Parameters

To explore the 24-h distribution of physiological parameters, we focused on 71 "nontravel days" by excluding the days when a time zone other than the home time zone was reported by the MOVES GPS parameter. To eliminate the possible effect from jetlag, we removed the entire last traveling day and also the following 2 d after travelling. (We note the results were very similar to those when no extra days were removed, indicating that the effect of jetlag on the patterns shown in Fig 2 are small (not shown)). The mean of the physiological parameters (measured by Basis Peak) for each hour per day were reported in the heatmap Figure (S2 Fig), and the overall hourly distribution of the 71 d was summarized in box plots (Fig 2). The sleep time per hour was defined as the percentage of times designated as sleep (Basis Peak) compared to the total number of hours (71 d) in each hour window. Either the standard time or the daylight saving time was selected in the analysis, depending on the time of the year.

Physiological Response to Different Human Activities

We binned the Basis measurements (HR, skin temperature, steps, and calories) into different activity categories (walking, running, cycling, sleep) according to the information from Basis and the MOVES app and compared the distribution in each bin (S3 Fig).

Flight Tracking and Cohort Information

Flight information was obtained using FlightAware (https://flightaware.com/). Flight information was accessed using the FlightXML API using Python SOAP client library Suds. For Participant #1, exact take-off and landing times (within 1 min) were recorded for >95% of flights.

For one out of the first 20 flights, SpO_2 was measured by Masimo device only at the cruise stage, and this is the flight that does not show inverse correlation between SpO_2 measurements and altitude.

Eighteen individuals participated in the flight study, and their age, ethnic background, and gender information are summarized in S1B Table. Participant #1 used Masimo, Scanadu Scout, and iHealth-finger device; Participants #16 and #44–#46 used iHealth-finger device; Participants #20, #47–#57, and #60 used Masimo device. Fig 4D shows the SpO_2 distribution for all the participants (shown for Participant #1 were data recorded by iHealth-finger device).

Assessing the Relationship between Tiredness and SpO_2 Levels

SpO_2 levels were measured by either Masimo or Scanadu Scout devices. Meanwhile, Participant #1 logged the status of "tired" and "alert," and we compared the wearable-measured SpO_2 levels between the two statuses according to the notes. To be more objective in defining fatigue, the participant also performed psychomotor vigilance test (Canadian tiredness test) (http://www.painfreesleep.ca/tiredness-test?&cid=semeOyQHbZq) in two separates flights besides the self-reported system. Specifically, this test evaluates the participant's fatigue status by measuring the participant's response time to a visual stimulus. For each measurement, response time to 12 visual stimuli were measured. Missed signal with response time slower than 500 milliseconds was counted as 500 milliseconds in the calculation.

Oral Temperature Measurement

The oral temperature of Participant #1 during Days 471–474 (Lyme disease infection) was measured by an oral thermometer (Day 471 8:00 A.M.: 100.7˚F; Day 471 7:00 P.M.: 100.2˚F; Day 472 8:00 A.M.: 98.9˚F; Day 473 11:00 A.M.: 100.7˚F; Day 474 3:00 P.M.: 102˚F; Day 474 6:00 P.M.: 101.4˚F).

Diagnosis of Diseases using Wearables-Measured Physiological Parameters

To investigate the ability of wearables to predict and monitor disease, a normalization framework was developed to accommodate the dynamic change caused by different activities and make measurements comparable. To normalize resting Basis-measured HR and skin temperature, we first excluded all the measurements recorded during or immediately after exercise that usually generate large variation in physiological parameters. Specifically, all records used have step measurements of zero for at least 10 min previous to that time point (including the current minute) and are also not associated with any prediction of activity (by MOVES software, if applied), including walking, running, cycling, or flying time (by personal calendar). Data in second resolution were first converted to minute resolution by calculating the median value. After filtering the activity-related data, we further performed Z-transformation (standardize) to the measurements based on the baseline norm of sleep status and nonsleep status (predicted by Basis device). Percentage-of-outliers was defined as percentage of measurements deemed outliers for each day by comparison with the personalized, activity-specific (sleep and nonsleep at resting) mean for the overall monitoring period (the baseline value; Z-Score >2). For Participant #58, whose sleep data are missing, the data were normalized based on the personalized 24-h distribution. Data from Basis B1 and Basis Peak were normalized separately to minimize the difference between devices. Overall, a period of 679 d (from Day 63 to Day 741) was examined. In this period, Basis data were missing for 76 d, therefore the analysis was performed on the remaining 603 d in this period. To capture data on both travel and nontravel

days, we defined the start and end of a day according to coordinated Universal Time, which is 7 or 8 h ahead of Pacific Daylight Time or Pacific Standard Time.

For the Day 470 flight, we assessed the Scanadu-measured SpO_2 readings (flight duration time = 94 min) relative to other flights by collecting all of the SpO_2 readings recorded by Scanadu during flights with similar flight time (duration time $<$120 min). The readings in each of the five flight stages were compared separately and the significance of the difference was assessed by two-sided Wilcoxon rank sum test.

For the analysis of illness with daily resolution, we detected abnormally elevated HR and skin temperature during the four periods reported. Specifically, we detected abnormally elevated HR (ranks #8, #2, #16, #3, and #1 out of 603 d, respectively) and skin temperature (ranks #1, #4, #10, #2, and #5 out of 603 d, respectively) for the period from Days 470–474; we detected abnormally elevated HR (ranks #7 out of 603 d) and skin temperature (ranks #12 out of 603 d) for Day 518; we detected abnormally elevated HR (Day 455 ranks #12 out of 603 d) and skin temperature (Day 456 ranks #6 out of 603 d) for the period from Days 455–456; we detected abnormally elevated HR (Day 667 ranks #4 out of 603 d) and skin temperature (Day 667 ranks #24 out of 603 d) for the period from Day 665 to Day 669.

To map inflammatory disease at higher resolution, we further analyzed the normalized HR. Specifically, we first smoothed the normalized HR using a moving average filter and then applied peak detection to identify local maxima of the smoothed signal. We used "smooth" and "findpeaks" packages in matlab to perform smooth and peak finding. To identify isolated peaks different from the global and local distribution at high confidence, we set "MinPeakHeight" to equal to two, "MinPeakDistance" to equal to "span" (3-h), and "MinPeakProminence" to equal to two. The optimized hyper-parameter "span" (3-h) was selected by training the model on Participant #1 and was applied when analyzing other individuals.

To evaluate the predictive power of the method in distinguishing the sick periods from the healthy periods, we defined a set of sick periods (positive set) based on self-reported symptoms and the relevant blood test. In the positive sets, we also included 3 d before the day when the symptom was reported or evidenced by blood work to acknowledge the fact that abnormal physiological signal might occur before the self-reported symptom. As a negative control, we followed the same rule and defined a set of periods either (1) composed of the days with normal CRP measurements or (2) composed of all days during the monitoring periods that are not included in the positive sets. We used binary scoring of each event by the presence or absence of the peak in the period. Each sick period was counted as one event. The area under the ROC curve was calculated to evaluate the classification power. We also employed cross-validation procedures to avoid overfitting to Participant #1's data.

Personalized Physiological and Activity Profiles for 43 Individuals

Of the 43 individuals tracked using Basis devices, 28 wore only Basis B1 devices, 9 wore only Basis Peak devices, and 6 wore both the Basis B1 and the Basis Peak. The Basis Peak has improved HR sensing during exercise as compared to the Basis B1; the resting HR and other parameters were comparable between the two devices. For the cohort-level analyses, 17.1 mo of Participant #1's data were used. We used activity normalization as well as device-specific normalization, as described below, to account for potential differences between the two devices. For each of the 43 individuals, we calculated average biometric values for HR, skin temperatures, and activity. For HR and skin temperature, we used measurements occurring at time points at which there were zero steps recorded at the current time point as well zero steps recorded within the 10 s previous to that time point. These periods corresponded to activity designations of inactive, light activity, and sleep by the manufacturer's algorithms.

The number of days recorded for each individual was calculated as the difference between the date the recording began and the date the recording ended or the date on which the data were accessed, whichever came first. We calculated the average number of steps per day for each of the 43 individuals by multiplying the average number of steps per second by the number of seconds in a day (86,400 s).

To capture daytime versus nighttime biometrics, we restricted our measurement capture window to 1 h during the day (3–4 P.M.) when our participants were awake and had taken more than 30 steps during this hour to guarantee a minimal level of activity, and compared this to 1 h during the nighttime (3–4 A.M.) when our participants appeared to be asleep and inactive with a threshold of less than five steps during this hour to ensure inactivity during sleep, but allowing for minimal measurement artifacts or limb movement during sleep.

Daily activity habit plots were created for each individual by generating smooth conditional mean lines with a 95% CI of accelerometer magnitude data by hour of day using generalized additive models (ggplot2 geom_smooth in R). Individuals were classified into one of four groups based on the peak characteristics of the curve. To automate this process, functional clustering using the R package FClust [57] was done on the activity curves to cluster members by similarity of activity curve characteristics (S2 Fig).

Comparison with Clinical Information

For the cohort that was monitored by the Basis devices, a subset of our participants had standard clinical panels (e.g., fasting plasma glucose, glycated hemoglobin [HbAlc], blood cell counts, etc.; S3 Table; performed in the Stanford clinical labs) and demographic information. The data were accessed using the Stanford Translational Research Integrated Database Environment (STRIDE) [58]. Thirty-eight participants with Basis datasets were annotated for gender (18 male and 20 female) and baseline BMI.

Twenty participants had undergone the modified insulin suppression test after an overnight fast (48). The test consisted of a 180-min octreotide (0.27μg/m^2/min), insulin (0.25 μg/m^2/min), and glucose (240 μg/m^2/min) infusion with blood draws at minutes 150, 160, 170, and 180. Blood glucose was measured using the oximetric method, and the SSPG is the mean of the four measurements [12,13,59]. IR is defined as a SSPG $\geq$140 mg/dL (n = 12), and insulin sensitivity is defined as $<$140 mg/dL (n = 8).

We analyzed average HR and skin temperature values for men and women using the 38 Basis datasets using an unpaired, two-tailed two-sample t test with Welch correction for potential unequal variation in the two populations. Pearson correlation between the average number of steps per day and average resting HR, as well as average number of steps per day and delta BMI (year 0 [baseline] minus year 1 BMI measurements) were done using R. The evaluation of the association between steps, HR (daytime, nighttime, and difference between day and night), and SSPG was done using SAS 9.4® (SAS Institute, Inc., Cary, NC. 2013). To account for unequal variances, we used a restricted maximum likelihood approach with a robust variance estimator to estimate the regression coefficients and their 95% CIs.

Supporting Information

S1 Fig. Accuracy of the devices. Bland Altman plots of the level of agreement between the Welch Allen clinical device and wearable sensors for SpO_2 (A) and heart rate (B). The difference histograms for SpO_2 (C) and heart rate (D) show percentage of measurements by level of difference between each of the wearable sensor devices and the clinical device. The SpO_2 number of measures per device is the same as those given by device for heart rate (D) with the exception of the Masimo device (n = 67 SpO_2). The Pearson correlation plots (E) show the

degree of correlation between the wearable sensor devices and the clinical device. Bland-Altman (F), Difference histogram (G) and Pearson correlation (H) plots of pair-wise comparison of step measurements between MOVES, Basis and Withings. In the Bland-Altman plots, the y-axis is the difference between both measurements and the x-axis is the average of the two measurements. The red line is the mean difference; the purple line and green lines are the upper and lower 95% limits of agreement respectively. The histograms provide a more quantitative measure of bias. In the Pearson correlation plots (E, H) symbol color represents number of overlapped points (blue: small number; magenta: large number). Measurements were done on a single individual (Participant #1).
(PDF)

S2 Fig. Circadian and Diurnal patterns in physiological parameters. (A-B) Heat map showing circadian changes in heart rates (A) and skin temperature (B) as measured using the Basis Peak device over 71 non-travel days. Measurements were done on Participant #1. The heat map of heart rates was organized by weekdays (A). (C) Four general daily activity patterns of the 43 study participants plotted according to actual values at the indicated times. (D) Functional Clustering (k = 4 groups) was done on the activity curves to automate the method of clustering members by the similarity of activity curve characteristics.
(TIFF)

S3 Fig. Physiological parameters change dynamically with human activity. Box plot shows dynamic changes of Basis-measured physiological parameters (A: HR, B: Steps, C: Calories, D: Skin temp) with different activities (Sleep category designated by Basis; walking, cycling, running categories designated by MOVES app). Data were collected on Participant #1.
(TIFF)

S4 Fig. Correlations between parameters measured by the Basis device. (A) Correlation between HR and Activity. The y-axis values are the mean of HR for each Activity ventile. The ventiles were binned based on accelerometer data for Activity. (B, C) Difference in mean HR (B) and Skin Temperature (C) between the highest decile and lowest quartile of Activity data, binned by accelerometer. The highest decile was used to capture higher impact activity (High Activity) while the lower quartile was used to capture low impact activity (Low Activity). Color shade represents the overall activity levels for each individual, with darker colors corresponding to the highest number of steps per day and lighter colors corresponding to fewer steps per day, ranging from 594 to 10,858 step/day for all individuals.
(TIFF)

S5 Fig. Investigating SpO_2 measurements during flight. (A) Example of SpO_2 measurements taken by Scanadu (blue) and iHealth-finger (red) on a typical flight. (B) Summary of distribution of SpO_2 values at different flight stages measured using the iHealth-finger device. (C) Box plot of the distribution of Scanadu-measured SpO_2 readings classified as "tired" or "work" from non-flying moments (left panel) and "tired" or "non-tired" at the cruise flight stage (right panel). Significance of differences was assessed using two-sided Wilcoxon rank sum test. (D) Scatter plot of response time and SpO_2 level recorded during one flight. The data recorded during another flight was shown in Fig 4F. Here, response time was derived from psychomotor vigilance test to objectively quantitate the tiredness of the subject. Cyan triangles, purple squares and red dots represent self-reported 'tired', 'in-between' and 'alert' status, respectively. (E) (Upper panel) Median SpO_2 level measured at the last quarter of the flight (yellow bars) and one of the other three quarters (blue bars). (Lower panel) Durations time of the flights. (F) CDF plot of Scanadu-measured SpO_2 levels $>$7hr after takeoff (red) vs. $<$2hr after take off (blue). All the data points were recorded at the altitude larger than 35000 ft. Significance of the

difference between the two distributions was assessed by two sample Kolmogorov-Smirnov test).
(TIFF)

S6 Fig. Relationship between flight altitude and SpO_2 measurement. Plot showing aggregate data from all flights (A) or short flights (B) with Masimo records for Participant #1. (C-G) Data from individual long flight Participant #1 took (only those with the complete record are shown). Symbol color indicates the time after departure. (H) Plot showing the relationship between the maximum altitude and the delta median SpO_2 for all participants with all flights. The delta median SpO_2 was calculated as the difference in median SpO_2 between the maximum altitude and at the ground. Each symbol represents a flight with Mamiso records. Multiple flights from one participate were shown by the same symbol with the same color. At personal level, a significant correlation was observed between the maximum altitude and the delta SpO_2 value for the two individuals with more than four flights (r = -0.52, P-value < 0.002; r = -0.86, P-value < 0.004, respectively). (I) As for H, but focusing on short flights. (r = -0.71, P-value < 0.004; r = -0.96, P-value < 0.0002, respectively).
(TIFF)

S7 Fig. Using wearables to assist disease diagnosis. (A) 679 day monitoring period for Participant #1. Left: elevated CRP periods; Right: fraction of outlying resting HR and skin temperatures (see Material and Methods). (B-C) Scatter plot of oral temperature and heart rate (B) and skin temperature (C) measured during the Lyme disease period. (D) Results from Lyme disease Antibody blot on Day 487. (E) CRP measurements are plotted against the proportion of daily skin temperature measurements that were more than two standard deviations above the mean for Participant #59 (F) CRP measurements are plotted against the proportion of daily heart rate measurements that were more than two standard deviations above the mean for Participant #37. (G) The timelines for the illness progression, CRP measurements, and Basis monitoring period captured in the figure are indicated for Participant #37. (H) Normalized HR at sick periods in minute resolution for Participant #37. Red peak: Abnormal periods indicated by the peak caller. Red vertical line: CRP larger than 2.5; Green vertical line: CRP larger than 1 but smaller than 2.5; Yellow vertical line: CRP smaller than 1. No peak was detected before the first CRP test since Participant #37 started to wear Basis device after the test.
(TIFF)

S8 Fig. Physiological summary of Participant #1. (A) Plot of fraction of outlying skin temperatures and heart rates for all 679 days of Participant #1. Connection was made by time. Line color indicates the health status (blue: health days; red: viral disease; yellow: high CRP event 1; purple: high CRP event 2; green: Lyme disease). (B) ROC curves showing classification power of the COH method in distinguishing the sick periods from the health periods. For each individual, two ROC curves are shown based on different definition of the negative set: (1) negative set was defined as days with normal CRP measurements (Participants #1, #58 and #59 and #37: purple solid line, AUC = 1); (2) negative set includes all the days in the measuring period which are not include in the positive set (Participant #1: red solid line, AUC = 0.983; Participant #58: blue solid line, AUC = 0.960; Participant #59: yellow solid line, AUC = 0.989; Participant #37: purple solid line, AUC = 1).
(TIFF)

S1 Table. Characteristics of our cohort. (A) 43 individuals participate in the analysis of personal baseline and health (B) flight study (C) Survey results to determine the location of the probe (inside or outside of the wrist, higher or lower on the arm, in the second column of the table) and whether the probe was always flush with the skin (based on tightness level of watch,

on a scale of 1–4, where the descriptors for each numerical value were: 1. Very loose (watch turns around sometimes); 2. Somewhat loose (1–2 fingers fit under band, but no watch turning); 3. Tight (can just barely fit 1 fingertip under band); 4. Very tight (cannot fit any fingertips under band, watch cannot be tightened any further).
(XLSX)

S2 Table. Summary of flights analyzed for SpO_2. (A) Participant #1 (B) Other 17 participants.
(XLSX)

S3 Table. Clinic test performed.
(XLSX)

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Value-Based Insurance Design: Benefits Beyond Cost and Utilization

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A decade ago, the concept of value-based insurance design (VBID) was conceived, based on the principle of aligning the clinical value of care for patients with consumer financial incentives, such as co-payments and co-insurance.[1] In the VBID paradigm, high-value, evidence-based services have lower cost-sharing levels, and low-value services have higher cost-sharing levels.[1]

In the years since its inception, various payers, firms, and government entities have implemented VBID programs.[2] For example, VBID has been incorporated into the Affordable Care Act via co-payment waivers for certain preventive services[3] endorsed by the Medicare Payment Advisory Council in reports to Congress as an approach to improve value,[4,5] and has been examined in the Institute of Medicine's report to the secretary of Health and Human Services on essential health benefits.[6] VBID principles are also growing in prominence: a survey of large firms revealed 81% were planning to incorporate VBID into their benefits packages in the future.[7]

Measuring the Impact of VBID Programs: A Spectrum of Dividends

As VBID programs proliferate, evidence is emerging on their impact. To date, studies have largely measured impact on utilization and a few have included quality, outcomes, and cost.[8] Here, we discuss these domains as well as our belief that the effects are likely to extend into related areas including work productivity, quality of life, engagement, and talent.

Several VBID evaluations have focused on measuring the effects of VBID on *healthcare utilization*, which includes medication adherence, guideline adherence, and medical care utilization.[8] These studies focus on the central mechanism of VBID: the price to the consumer. In response to a change in price, utilization of these services is likely to change. Measuring the impact on utilization is essential as it provides information on the central question surrounding the effectiveness of the VBID program: is the core principle of the program working as intended?

ABSTRACT

As value-based insurance design (VBID) programs proliferate, evidence is emerging on the impact of VBID. To date, studies have largely measured VBID impact on utilization, and a few studies have assessed its impact on quality, outcomes, and cost. In this commentary we discuss these domains, summarize evidence, and propose the extension of measurement of VBID impact into areas including workplace productivity and quality of life, employee and patient engagement, and talent attraction and retention. We contend that VBID evaluations should consider a broad variety of programmatic dividends on both humanistic and health-related outcomes.

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Take-Away Points

Value-based insurance design (VBID) evaluations should consider a broad variety of both humanistic and health-related outcomes.

- Previous studies have explored the impact of VBID on utilization, and a few have included healthcare quality and outcomes.
- Additional domains of benefit include workplace productivity and quality of life, employee and patient engagement, and talent attraction and retention.

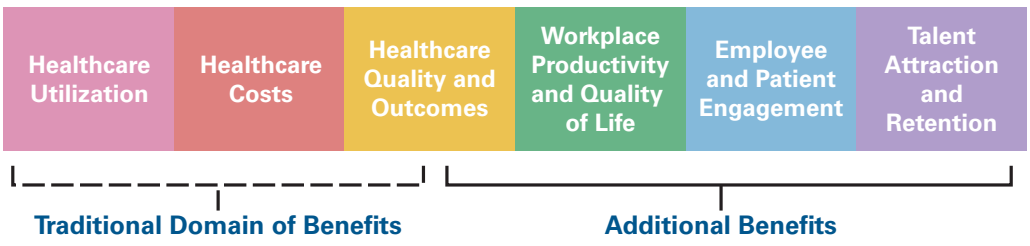
A 2013 review found that VBID programs were associated with a 3% increase in medication adherence on average,[8] and a more recent study reported similar findings from a VBID program implemented within a large health plan, showing a 2.7% to 3.4% increase in adherence.[9] Two VBID studies analyzed medical service utilization, with the first study reporting a significant first year decrease in emergency department (ED) visits and physician office visits for patients in a diabetes VBID, and in the second year patients with diabetes experienced a significant decrease in ED visits.[10] Hospital admissions were unchanged in the first and second years. The second study reported reductions in ED visits, hospitalizations, and physician office visits for users of certain medications included in the VBID program.[11]

Few studies have extended measurement of VBID effects to include *healthcare quality* and *outcomes*, incorporating clinical measures such as patient laboratory values, complications, and mortality into a VBID assessment.[12] This approach focuses on outcomes of care and the quality measures most likely to be affected by utilization of VBID services. For example, reduced cost sharing for diabetes medications has been shown to increase adherence,[13-15] and based on empirical evidence, patients with higher levels of adherence can experience better outcomes, including complication rates (eg, heart attack, stroke). Improvements to the process of care and to management of care could be ascertained through changes in quality measures related to high-value services, such as the Healthcare Effectiveness Data and Information Set measure assessing persistence of beta-blocker treatment after a heart attack.

In terms of evidence, a randomized VBID intervention waiving co-payments for preventive medications after heart attack (the "Post-Myocardial Infarction Free Rx Event and Economic Evaluation" [MI FREEE] trial) reported a decline in total major vascular events and revascularizations, as well as in the rate of occurrence of initial major vascular events.[12] A secondary analysis from the MI FREEE trial also found a reduction in disparities in outcomes of care.[16] For subjects identifying as nonwhite, the co-payment waiver was associated with reductions in rates of revascularization and major vascular events, although not among subjects identifying as white. In addition, a prepost study of a combined pharmacist intervention model with a VBID diabetes medication co-payment waiver showed a 17 percentage point increase in patients with a glycated hemoglobin value of ≤7.0; however, the study was uncontrolled.[17]

A few studies have focused on *cost impact* based on changes in direct medical spending.[8] In general, measurement of the economic impact is not straightforward and can vary depending on the perspective adopted (eg, patient, health plan, employer) and the extent of measurement (eg, direct medical costs, indirect costs, program costs). For example, if co-payments are lowered for high-value medications, then direct medical spending on these medications will decrease for the consumer. In contrast, the health plan is likely to experience higher direct spending on these medications due to higher payment rates and higher rates of utilization. At the same time, direct medical spending by the health plan could be reduced by short- or long-term savings in medical spending from any cost offsets resulting from lower complication rates. Additional programmatic costs to design and implement the VBID are likely to be incurred, as well as potential savings in indirect costs from changes in work productivity. Evidence to date shows that VBID programs are associated with a reduction in patient out-of-pocket costs for VBID

Figure. Spectrum of Dividends



services. Notably, existing VBID programs have not been associated with changes in total medical spending.[8,9,12]

The association between VBID and *work productivity* or *quality of life* is a natural extension due to the close ties among health, productivity, and functional status; because VBID is health-enhancing, work productivity in participants is likely to improve. For example, improved adherence to medications to treat diabetes, hypertension, hyperlipidemia, asthma, and chronic obstructive pulmonary disease has been associated with improvements in work productivity.[18] The theoretical relationship between VBID and productivity has been well addressed,[19,20] although empirical verification has not yet occurred.

Also unexplored are the effects of VBID programs on patient *engagement* in health and wellness. Engaged employees are marked by characteristics such as commitment, vigor, dedication, and absorption.[21] Engagement in work and in one's own health has been linked to better health outcomes because engaged employees are more likely to have better health outcomes and more importantly, better experiences with care provision.[22] It remains to be proven that when, for example, price incentives are applied to high-value services (eg, adherence to a regimen of care for a chronic condition), a patient utilizes more of these specific services and becomes more actively engaged in health management and wellness. In response to VBID, patients may gather relevant information, including data about their own health status (eg, biometric measures), health conditions, and appropriate treatments and actions. We contend that patients who are well informed and participate in their care in coordination with their provider are more likely to stay abreast of treatments that are considered high value or evidence-based, and are more likely to improve or maintain health.[23-26] These patients are more likely to exhibit high health literacy, healthy behaviors, and greater productivity.

A final unexplored dimension of benefit of VBID for workplace programs is the impact on a firm's *talent*. Offering enhanced or individualized benefits could improve recruitment or retention, as employees or their family members receive a package of benefits aligned with their needs.[27] However, this approach could also result in selection effects, as good potential employees might not choose to work at a firm with non-VBID plans. In addition, emphasizing the corporate value of health and wellness may also serve to attract and retain employees who place a great deal of value on health and wellness.[28]

Additional Initiatives to Improve VBID Effects

VBID is not intended as a stand-alone lever to produce positive effects; it can be used in synergy with other initiatives such as wellness programs,[29] integrated health systems, and health information technology to enhance results. These activities may also include regular information-gathering from biometric screenings, assessment of results from health risk appraisals, and discussions of health risks and disease state(s) from well-structured patient-provider interactions.[26] At a minimum, these services could be used to identify diseases and risks to create an individualized list of high- and low-value services. For example, a patient with undiagnosed high blood pressure is not likely to respond to VBID financial incentives for treatment of hypertension. A likely responder is a well-informed, engaged hypertensive patient with a benefit program designed to provide information about blood pressure readings, cardiovascular risks, a medication management plan, a program of lifestyle change, and frequent interactions with care providers.

Next Steps

We provide this overarching framework to capture the *spectrum of benefits* that may result from VBID programs, extending beyond utilization and outcomes to positive impacts on work productivity, employee engagement, and talent management. VBID evaluations should consider a broad variety of programmatic dividends on humanistic as well as health-related outcomes.

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The Columbus Dispatch

Pediatric Research: 'Team science' approach has changed research

Saturday
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The image of a scientist as a solitary, geeky figure hunched over test tubes in a lab does not reflect reality in today's world. Medical research increasingly is social and collaborative. People skills and expertise in communication are crucial.

The image of a scientist as a solitary, geeky figure hunched over test tubes in a lab does not reflect reality in today's world. Medical research increasingly is social and collaborative. People skills and expertise in communication are crucial.

These skills are important because today's research is most effective when it is designed to involve many different scientific disciplines working in a highly coordinated way to solve the most-challenging health problems of our time.

Team science is the term often used to describe this type of endeavor.

The change in the way biomedical research is conducted has occurred because the tools of that research are varied, complex and sophisticated. One person, no matter how talented and hard-working, cannot get the job done alone.

A great example of team science that included cancer experts at Nationwide Children's Hospital and Ohio State University was published recently in the *New England Journal of Medicine*. The research reports breakthrough genetic findings in 1,725 children and young adults with acute lymphocytic leukemia.

There were 70 authors of the study. To place this in context, the average number of authors listed per article in the PubMed database of medical research publications in 2013 was 5.4. In 1913, it was one.

The 70 authors involved in the leukemia research work at universities and research centers in 22 cities in three countries. Three are from the Research Institute at Nationwide Children's, and four work at Ohio State's Comprehensive Cancer Center.

The department affiliations of the 70 authors reflect the diversity of scientific disciplines and include pediatric cancer, adult cancer, biostatistics, epidemiology, computational biology and pathology. The work included both clinical experts and lab scientists.

Imagine the planning needed for a research study such as this. Team members are located in different cities and have divergent backgrounds. Some probably have worked together before, but most have not. Just imagine the bureaucratic and administrative obstacles as well as the formidable communication challenges.

Millions of dollars are at stake, and lives literally hang in the balance if the project team poorly executes the game plan.

The trend in the United States and other developed countries is for a growing number of authors on biomedical research papers and an increase in the proportion of papers co-authored by scientists from different countries.

Scientific papers with greater numbers of authors are referenced more by other scientists and are also more likely to be published in prestigious journals.

The National Institutes of Health is hosting a team science conference this summer to examine practices that contribute to efficient and effective research collaborations.

Science and scientists aren't what they used to be. Team-based science increasingly will become the norm as we capitalize on the gains in genomics, big data and other complex fields.

The way we train scientists, organize research studies and recognize credit for team science must evolve to keep up with this important trend.

Dr. John Barnard is president of the Research Institute at Nationwide Children's Hospital.

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Return on Investment - Know Your Project's Value

Return on investment (ROI) is a useful tool for understanding a project's costs and benefits from the perspective of an investor. Government officials such as governors and mayors (for public health agencies) or chief financial officers (for healthcare systems) might ask what the expected value of a collaborative project is, or, what is the value proposition? In fact, particularly in the private sector healthcare system, they are specifically likely to want to know the return on investment (ROI). A collaborative project's most significant outputs are likely to be nonfinancial benefits realized by patients, communities, and society as a whole (e.g., improved provider–patient relationships, increased quality of care, prevention of illness, and improved quality of life). At the same time, some of these projects might also produce a financial ROI for profit-motivated investors, and healthcare system leaders can use that to incentivize their support of collaborative projects with population health goals. As part of the planning process, it's important to define all costs and benefits, including projected cost savings and health outcomes, for different types of stakeholders, to ensure ongoing support from decision makers and, thus, sustainability.

Tips

In thinking about, promoting, and evaluating the value produced by a collaborative health improvement project:

- Take into account not only direct financial benefits to investors, such as payers' lower healthcare delivery costs, but also the nonfinancial benefits provided to the community: the project's *social* return on investment.
- Keep in mind that the value of a community health improvement initiative largely depends on whether its benefits are considered from the perspective of patient, physician, community, local (public health) government, or health services purchaser. Strive to identify project benefits accruing to as many stakeholders as possible.
- In designing interventions for a collaborative project, consider including low-cost, high-impact components along with those intended to produce benefits over the long term.

Use the following tools and guides to assist with understanding and calculating return on investment for your collaborative project:

- Estimating Return on Investment for Public Health Improvements: Tutorial on Using the New Tool
- Rapid Response Team Return on Investment Calculator
- AHRQ's Asthma Return on Investment Calculator
- Medicaid Return on Investment Template

What is "Return on Investment"?

Return on investment (ROI) is a useful tool for understanding a project's costs and benefits from the perspective of an investor. ROI analysis originally was developed in a commercial business context to assess the performance of a financial investment. Its focus is the financial return that a specific investor receives from his/her own financial investment. A simple ROI equation, for example, shows that an investor who purchases goods for $1 and resells them for $3 receives a 200% return on the cost of the initial investment.

$$\frac{Proceeds\ of\ investment\ [\$3] - \ cost\ of\ investment\ [\$1]}{Cost\ of\ investment\ [\$1]} \times 100\% = ROI\ [200\%]$$

In healthcare, ROI usually refers to the financial costs to a specific payer or healthcare system, because it is the payer or institution that wants to know the value to itself of any investment. For many healthcare payers, the period over which ROI is calculated is short due to high rates of turnover in health plans; payers cannot recoup the costs of prevention or disease management if people are no longer enrolled in their plans. However, each plan may differ in terms of time frame. Medicare takes a relatively long time perspective, typically 10 years.

ROI can have multiple meanings. It can be used to refer to the financial return to a particular state agency, to all state/local agencies, or to government as a whole. The last is sometimes referred to as the taxpayer perspective, even though it's not from the viewpoint of taxpayers as individuals. It includes spending on non-health services, such as public assistance and schooling, and also impacts on revenues from taxes paid by people who might otherwise not be able to work. A societal perspective ROI should include all financial costs and benefits regardless of who receives them or pays for them. It includes government programs, businesses, and individual consumers, and is therefore more complete.

Consider an asthma education program that costs $500 per asthma patient and, on average, avoids a single emergency room visit cost of $1,500. Assume that the cost of the program is paid by the public health department and the benefit accrues to a payer. From the public health department's perspective, the cost is $500 per person served with a zero (0%) return. From the payer's perspective, there is no cost of the education program but a net savings of $1,500 per enrollee, all return. If Medicaid is the payer, the ROI in terms of total health expenditures is 200% [($1,500–$500)/$500] — a great investment! Similarly, if either Medicaid or a private payer were to pay for the asthma education program, the ROI to the payer would likewise be 200%. The societal ROI is difficult to calculate because potential impacts other than reduction in emergency department visits would need to be considered (Table 1).

Table 19-1. ROI From Different Perspectives			
Perspective of Agency/Individual	**Cost of Educational Program**	**Emergency Room Cost Saved**	**ROI**
Public Health Department (PHD)	$500	$0	0% (0-$500)/$500
Payer (PHD pays for the program)	$0	$1500	ROI can't be calculated because there is no payer investment
State health programs (PHD, Medicaid pay)	$500	$1500	200% ($1500-$500)/$500
Payer (Payer pays for the program)	$500	$1500	200% ($1500-$500)/$500
Societal (PHD pays for the program)	$500	$1500	ROI can't be calculated without additional information on benefits

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What about Cost-Benefit Analysis (CBA)?

The interests of investors in a public health project are different than those of individuals and entities that invest primarily to generate profits. Most public health projects yield primarily nonfinancial benefits (such as improved health or cases of illness prevented). These projects' benefits accrue to patients, communities, and society as a whole. In a CBA, though, the value of those non-financial benefits needs to be expressed in terms of their dollar value. In addition, public health projects may also have financial benefits, such as healthcare costs averted or increased productivity. When project costs are considered from a societal perspective, rather than an ROI, a simple cost-benefit analysis (CBA) can be used to assess whether the project's benefits justify its costs. If the intervention costs $1,000 to implement and achieves improved health outcomes valued at $2,000, the project has a net benefit.

CBA: Benefits [$2K] – Costs [$1K] = $1K net gain

A cost-benefit analysis attaches dollar values to all costs and benefits of a project. Costs are not limited to monetary outlays; they include costs related to human effort (staff time devoted to the project), costs related to the project's use of physical resources (meeting space, equipment), and lost opportunity costs (foregoing potential gains from other possible investments). Benefits, particularly in the case of health interventions, include not just the project's financial outputs, but, often more importantly, its non-financial, *social* benefits (improved patient and population health, better healthcare quality, improved accountability for government resources). In a CBA, all non-monetary costs and benefits, including these social impacts, are assigned a monetary value.

What is Cost Effectiveness Analysis (CEA)?

The costs of a project involving public health and primary care collaboration are often shared among multiple sponsors with varying interests and perspectives. Its benefits might be diffused among patients, providers, payers, the community, and society. Depending on its goals and expectations, financial or social returns may be more or less important to a particular sponsor. A cost effectiveness analysis (CEA) examines the costs and outcomes of alternative intervention strategies, and can be used to facilitate decisions about potential approaches for a given health outcome. CEA compares the cost of an intervention to its effectiveness as measured in natural health outcomes (e.g., "cases prevented" or "years of life saved"). The results of a CEA are expressed in cost per health outcome (e.g., cost per case prevented or cost per workdays gained). CEA does not require a monetary value to be assigned to health outcomes. A CEA is often

expressed as a cost per quality-adjusted life year (QALY) gained, where QALYs are a combination of improved quality of life and number of years of survival gained; this is also called a cost utility analysis and allows comparison of different health outcomes. In contrast to CBA, CEA does not require a monetary value to be assigned to health outcomes.

When applied prospectively, cost effectiveness analysis helps planners choose between different approaches to achieving a desired outcome, and which of several proposed interventions is likely to produce the most value. By taking into consideration all of the project's costs and benefits, and the perspectives of all potential sponsors, the analysis can help answer questions such as:

- Do the project's expected benefits justify its implementation costs?
- Which project will produce the greatest impact?
- Which potential sponsors are most likely to support the project?

Cost effectiveness analysis also can serve as a powerful tool for policy development when used to demonstrate to decision makers and the public the financial savings and social value to be gained from investments in population health, health system transformation, quality improvement, and public health–primary care collaboration. Though some programs and policies save money, many do not. As in most things in life, the question is whether those programs and policies are worth the investment.

Which Economic Evaluation Method to Use?

A Comparison

For any economic analysis, it's critical to understand the included costs and benefits. Table 2 compares basic characteristics of different approaches. It's common for analyses claiming to take a societal perspective to include only a small subset of benefits. For example, an analysis of the financial return on investment for patients enrolled in the Boston Children's Hospital Community Asthma Initiative was described as a cost-benefit analysis even though it only included the avoided costs of hospital care as benefits, and did not include the monetary value of health outcomes or of other societal benefits. A similar analysis of another asthma disease prevention program was correctly described as an ROI analysis.

Table 19-2.

Overview of Types of Financial and Economic Evaluation

Type of Analysis	Definition	Typical Costs	Typical Outcomes	Metric	Typical Use
Return on investment (ROI)	A financial analysis from the perspective of the investor	Dollars invested	Dollars saved	Net financial cost/dollars invested	To assess financial return
Cost-benefit analysis (CBA)	An economic evaluation that assesses the dollar value of all resources used and benefits achieved from the perspective of society	Dollar value of all resources used	Dollar value of all health and non-health outcomes	Net cost (dollars)	To compare the value of policies and programs with different outcomes, particularly when there are both health and non-health effects
Cost-effectiveness analysis (CEA)	An economic analysis that assesses the net cost of an intervention compared to the health outcomes achieved (perspective must be specified)	Dollar value of resources used	Health benefits (eg, deaths averted)	Cost per health benefit (eg, cost per life year gained)	To compare the value of policies and programs with the same health outcome

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Case Illustration: Projected Value of Diabetes Prevention

Preventing diabetes presents a major opportunity to reduce healthcare costs through a collaborative partnership. The Diabetes Prevention Program (DPP) is an effective model to prevent diabetes through intensive dietary and physical activity counseling, and illustrates the importance of including all perspectives when considering the costs and benefits of a collaborative project. The original DPP was an intensive clinic-based research study. The intensive lifestyle arm of the study was shown to be highly effective in leading to large weight reductions in overweight adults with pre-diabetes, and incidence of diabetes was reduced by 58% over a 3-year period. The original intervention was found to be highly cost-effective from the long-term, societal perspective, costing a little over $1,000 per QALY gained, but from the short-term financial ROI perspective of a private health plan, it would return only 24 cents on the dollar within a 3-year time frame. An adaptation using group-based counseling delivered though a community-based organization was found to cost less than one third as much.

An adaptation of the DPP intervention using group-based counseling delivered though a community-based organization (the YMCA) following clinician referrals of overweight patients with pre-diabetes was found to be feasible and to cost less than one third as much as the clinic-based DPP. In 2010, Congress authorized the CDC to establish the National Diabetes Prevention Program (National DPP), which brings together community and healthcare organizations, insurance companies, employers, and government agencies to implement the lifestyle intervention across the U.S. The inaugural partners joining the CDC in the National DPP were UnitedHealth Group (UHG) and the YMCA of the USA. They rolled out the adapted DPP in 46 communities between July 2010 and December 2011, and 1,723 participants completed the program at an average cost of $400/person. UHG projected that avoided healthcare costs would exceed intervention costs within 3 years. Currently, over 500 organizations have received CDC recognition as part of the National DPP.

Two simulation models based on the YMCA DPP model calculated that this group-based lifestyle program is eventually cost-saving at a national level. One model projected the costs and benefits of adapted DPP to the U.S. healthcare system as a whole using conservative assumptions and concluded it would break even in 14 years; within 25 years it could produce societal savings of $5.7 billion nationwide. That model, unlike other analyses, included the costs to detect pre-diabetes in adults through screening of overweight adults by primary care providers. Another simulation model concluded that referring overweight adults aged 60 to 64 years to such group counseling could be cost-saving to the Medicare program in well under 10 years. A larger-scale study of the YMCA DPP program is currently underway to produce more robust estimates of costs, effectiveness, and cost savings.

Although the exact length of the payback period for the community-based DPP model to generate negative net healthcare costs remains to be determined, it is clearly cost-saving to the U.S. healthcare system overall, and to payers such as Medicare that take a relatively long-term (i.e., 10-year or longer) perspective. As such, it is a worthwhile priority for public health–healthcare collaborations aimed at improving population health and controlling healthcare costs.

Conclusion

Understanding the economic consequences of collaborative projects to each stakeholder, as well as to communities more broadly, can help in the design of programs and enhance the likelihood of success and sustainability.

Adapted from Chapter 19: Teutsch, Steven M.; Koo, Denise; and Grosse, Scott D. "Return on Investment and Economic Evaluation." In The Practical Playbook: Public Health and Primary Care Together, edited by J. Lloyd Michener, Denise Koo, Brian C. Castrucci, and James B. Sprague, 225-234. New York: Oxford University Press, 2016.

Related Insights

ASTHO's Phased Approach to Funding Support (/page/asthos-phased-approach-funding-support)

Diversified Funding for Sustaining your project (/page/diversified-funding-sustaining-your-project)

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LOGISTICS INFORMATION

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Board on Health Sciences Policy | Roundtable on Genomics and Precision Health

MEMORANDUM

TO: Invited Speakers of the Roundtable on Genomics and Precision Health
FROM: Meredith Hackmann, Research Associate
DATE: March 1, 2017
SUBJECT: Logistics and Travel Information – *Spring 2017 Meeting of the Genomics Roundtable*

Please RSVP here to notify me of your attendance and hotel needs.

Date/Time: **March 9, 2017** **8:15 A.M. – 3:45 P.M.**

Location: **Keck Center**
Room 100
500 Fifth Street NW
Washington, DC 20001

Agenda: On **Thursday, March 9,** the Roundtable on Genomics and Precision Health will hold a meeting from **8:15 A.M. – 3:45 P.M.** Breakfast will be available starting at 7:45 A.M. Lunch will also be provided.

Travel and Reimbursement:

If your place of business is more than 50 miles from the Keck Center, the Academies will reimburse you after the meeting via a Travel Expense Report (TER) for *reasonable* travel expenses as described below. Please retain all receipts for expenses incurred during travel on Academies business. **Any charges exceeding $75 MUST include a receipt.** This includes items such as airfare, parking, and taxi charges. ExpenseIT® Pro (a free app that can be downloaded from iTunes or Google Play) allows you to take pictures of your receipts on your phone and automatically create expense entries in Concur. Reimbursement will come via check to the address you have listed with the Academies unless you have a direct deposit arrangement in place.

TRANSPORTATION

Air and train travel MUST be made through Uniglobe Kentlands Travel if you are supported by the Genomics Roundtable. Travel booked through Kentlands ensures compliance with all travel policies and access to negotiated rates.

Phone: 301-948-2448; toll-free: 1-800-552-6425 | **Email:** nas@uniglobekentlands.com
After hours or Emergency: 888-565-9174.

Please refer to travel code **HMD170037** when making travel arrangements. If you book through Kentlands and experience any problems, you may contact them 24 hours a day.

Generally, the Academies' payment of travel expenses is limited to the cost of a ticket that meets the following criteria:

- Economy class or coach (train)
- Non-refundable
- Within the approved travel dates (one day before and after the meeting)
- Roundtrip from your usual place of business to the meeting site
- No additional stops for personal or business reasons

Upgrading seats at personal expense is permitted, including through the use of frequent flyer miles. A proposed coach-class itinerary that shows the coach-class fare must be attached to the TER.

Please note that no changes in tickets for travel reservations will be paid for by the Academies except in the case of a documented emergency. **Therefore, please understand that we will not be able to pay for changes due to scheduling issues.** Any change to your ticket will need to be accompanied by an explanation of the emergency necessitating the change. All change fees are subject to approval by the Academies.

If you will be driving to the meeting in lieu of air or rail travel, please note that the current rate for reimbursement of mileage for a personal vehicle is 0.56 cents per mile. A comparative cost must be obtained and your reimbursement will be limited to the cost of roundtrip air travel.

Making Stops En Route

If you need to make an additional stop or stops en route to the meeting or after the meeting, please let me know in advance via email so we can determine comparative costs for reimbursement. You will be reimbursed for the cost of a direct round trip ticket between your permanent place of business and the meeting location or the face value of the ticket, whichever is less. If you expect to be reimbursed by a third party for any part of your travel, costs should be allocated appropriately. The constructive cost of direct travel must be based on the most economic fare and must be established prior to travel reservations being made. If the constructive cost is not determined in advance, it will be determined by the Academies by referencing the lowest reasonable cost available after the fact by the Academies Travel Office, which could potentially lead to a reimbursable amount lower than the actual price of the ticket.

REIMBURSABLE EXPENSES

Examples of out-of-pocket reimbursable expenses include:

- Airport parking fees
- Meals not provided by the Academies (see per diem guidelines below)
- Taxi cabs, shuttles, and public transportation
    - Sedan services are only reimbursable if the cost is comparable to a taxi fare
    - Car rentals <u>are not</u> reimbursable in DC
- Internet access charges at the hotel (if not included)

PER DIEM

We are required to follow the federal government's per diem guidelines for purposes of reimbursement. In Washington, DC, the maximum per diem is **$311**, which includes **$242 for lodging**

and up to $69 per day for meals and incidentals. On a travel day, your reimbursable amount will be $51.75 (75% of the per diem rate) for meals. Meals provided during the meeting are included in per diem allowances. Please note that the Academies will reimburse the *actual* cost of meals rather than a flat per diem rate.

Hotel

A block of rooms has been reserved at the **Embassy Row Hotel** (2015 Massachusetts Avenue NW, Washington, DC 20036). The hotel is located three blocks from the Dupont Circle Metro Station (Red Line), which is four stops from Judiciary Square. The hotel is approximately a 15-25 minute taxi ride to the Keck Center.

The cost of your hotel room will be billed directly to the Academies based on the dates you specified on the registration form; however, incidental expenses (room service, parking, etc.) will need to be settled during checkout. If your plans change and you no longer require a reservation, please contact me as soon as possible to avoid charges for unused rooms. If you choose a different hotel, it is important to take the per diem amount into consideration since you will not be reimbursed for expenses exceeding that amount.

You will receive instructions on submitting your expenses online via email after the meeting. TERs must be submitted within 30 days of travel.

Staff contact information

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Directions to the Keck Center of the Academies
500 Fifth Street, NW, Washington, DC

The Keck Center is located in downtown Washington, DC at 500 Fifth Street, NW, diagonally opposite the Verizon Center and the National Building Museum. It is on the block bounded by Fifth and Sixth Streets and E and F Streets; the only other building on the block is a fire station on the corner of Fifth and F Streets.

Building Entrances, Security, and Directions:

If you are arriving by cab or by Metro, the *pedestrian* entrance is on the Fifth Street (east) side of the building, just past the fire station.

If you are *driving* to the meeting, the *garage* entrance is located on the Sixth Street side, near the north end of the building. Before entering the garage, stop at the security check point. You will be asked the nature of your business and to show ID before entering. If you are planning to drive, please let a staff member know in advance, so your name can be provided to security personnel. Limited guest parking is available on the first level; take the visitors' elevator up to the lobby level and sign-in. Please be aware that parking is allocated on a first come basis and staff cannot reserve spaces for guests.

Arriving by Metro:

NOTE: Metro track work will be in effect during the meeting and could disrupt travel and generate heavier traffic. More information can be found here.

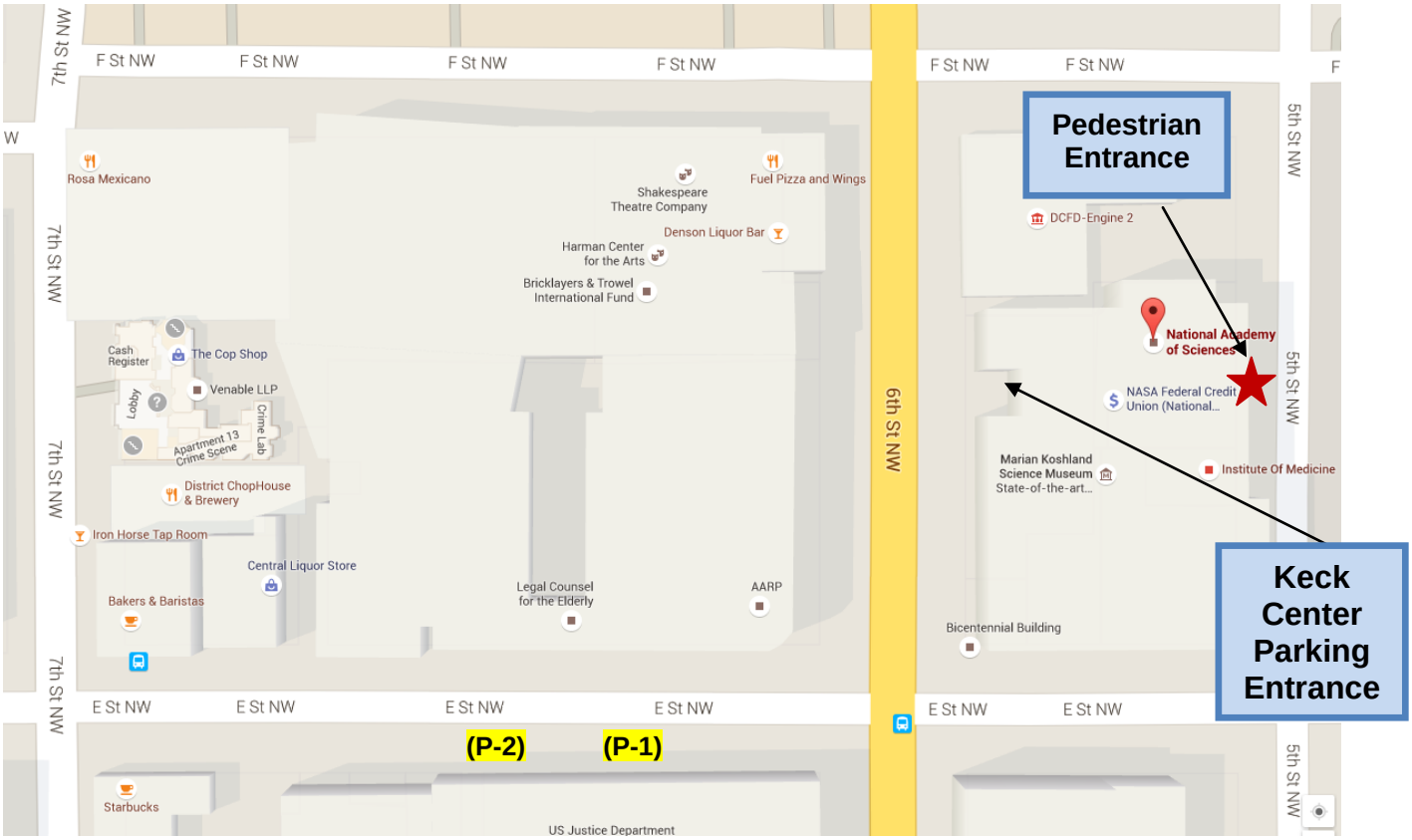
Take **Metro's Red Line** to the **Judiciary Square** station. Exit the station by following signs to the Building Museum/Arena/Police Memorial (F St.) exit, between Fourth and Fifth Sts. NW. Turn LEFT and walk WEST on F St. NW. Cross Fifth St. NW and turn LEFT. Walk past the fire station parking lot. The next building on your RIGHT will be 500 Fifth St. NW. (Note: Union Station is on the Red Line).

Take **Metro's Green or Yellow Line** to the **Gallery Place-Chinatown** station. Exit the station by following signs to Seventh and F Streets/Arena. Turn LEFT and walk EAST on F St. NW, two blocks past the Verizon Center. Turn RIGHT on to Fifth St. NW. Walk past the fire station parking lot. The next building on your RIGHT will be 500 Fifth St. NW. [Note: Ronald Reagan Washington National Airport station is on the Yellow Line.)

Additional Parking - IF Keck Center parking lot is full - See map below
Prices are subject to change.

(P-1) Parking Garage on 600 E St NW, Washington, DC - $15.00, 8AM to 6PM.
Laz Parking Mid-Atlantic Inc. - (202) 393-1966.

(P-2) Parking Garage on 616 E St NW, Washington, DC
Building right next to 600 E St., NW.



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