Personalized medicine:
Screening version 2.0
and a new era of overdiagnosis

Henrik Vogt
General practitioner, MD, PhD
NTNU Norwegian University of Science and Technology
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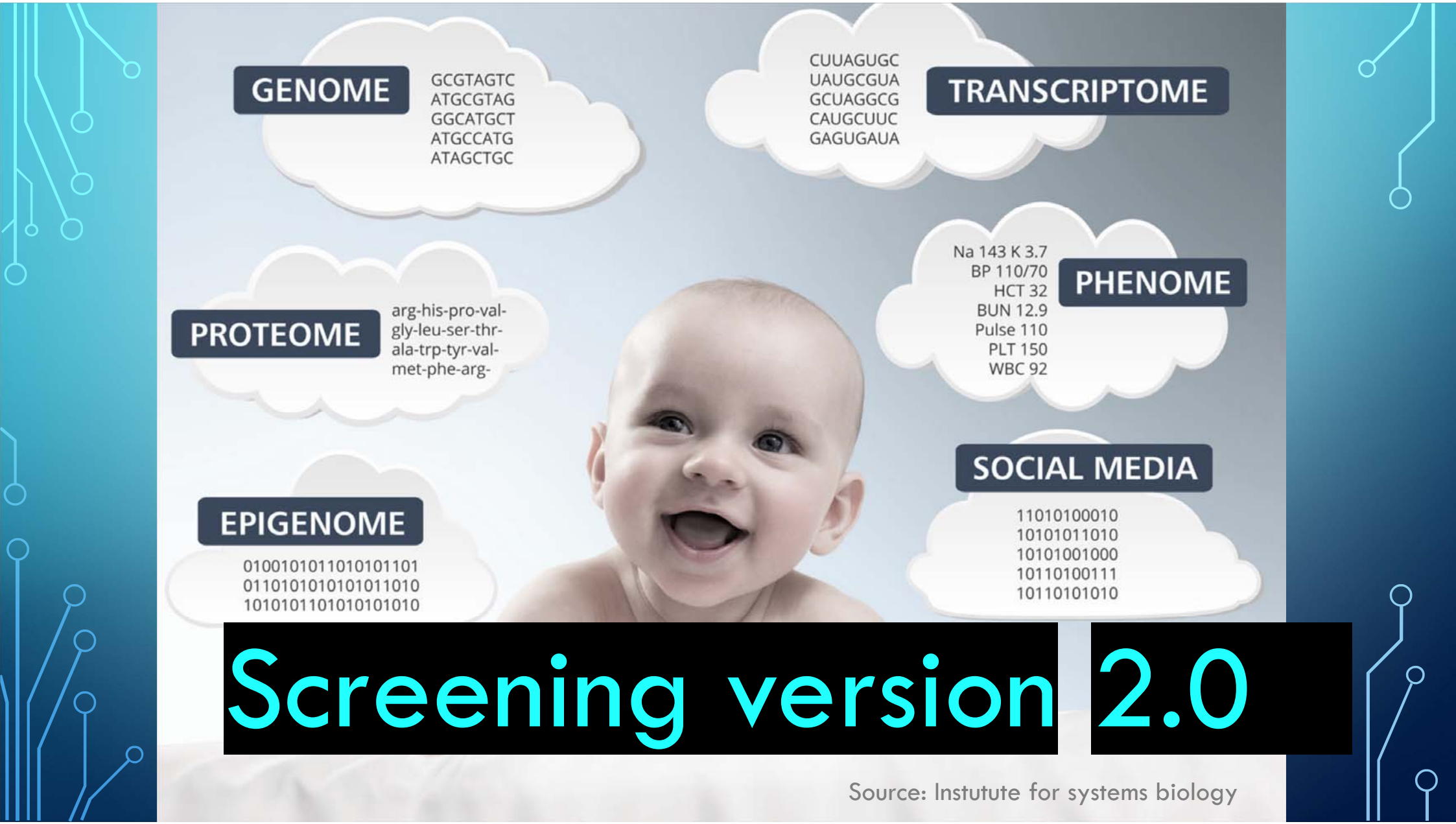
Store Praksisdag 2019
- Patienten der udfordrer os



Screening version 2.0

Source: Instutute for systems biology

VISIONEERING: THE SELLING OF «PERSONALIZED»

I will talk about what is mostly A VISION. Why?

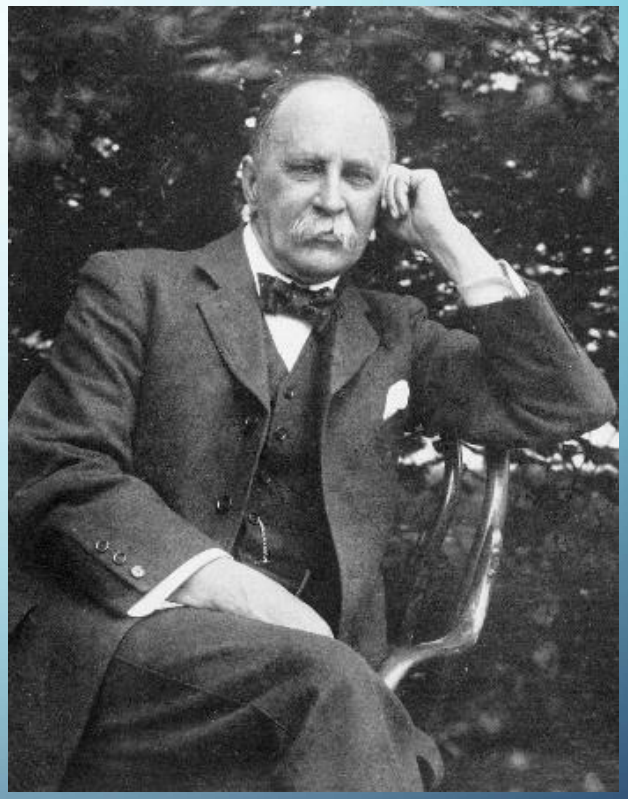
Visions are powerful.

«Visioneering».

My PHD is a critique of the personalized medicine vision.

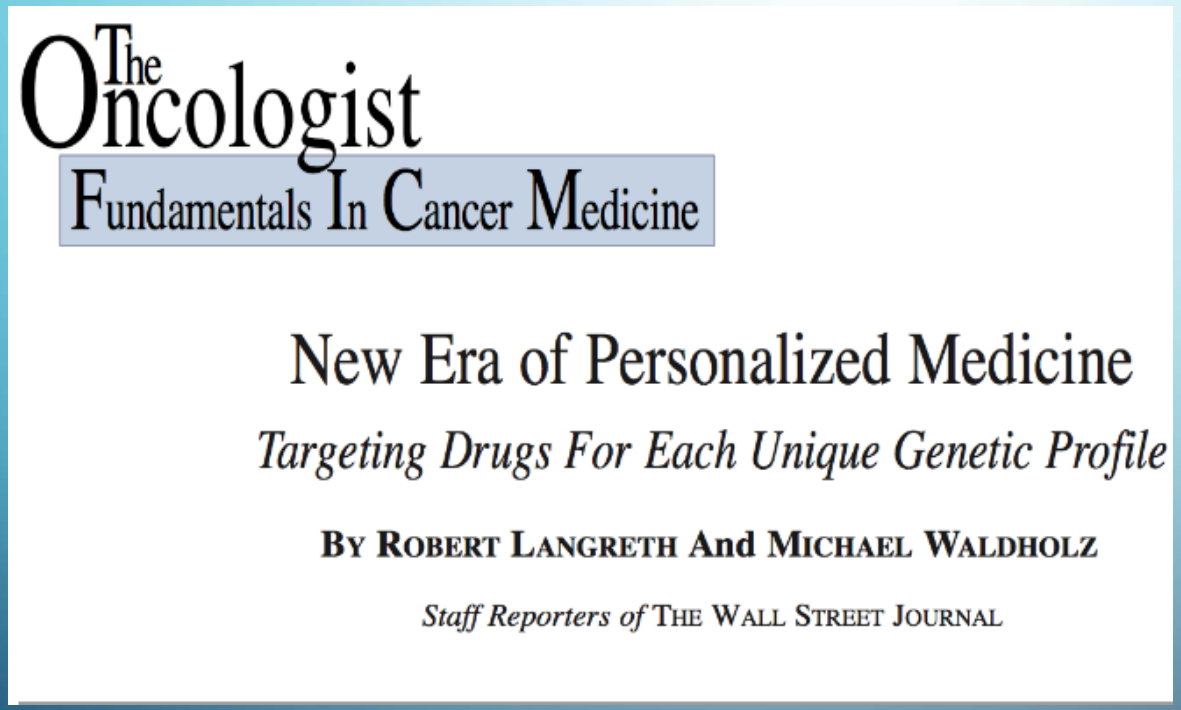
PERSONALIZED MEDICINE

"If it were not for the great variability among individuals, medicine might as well be a science and not an art".



William Osler (1849-1919)

PERSONALIZED MEDICINE/PRECISION MEDICINE



The Oncologist

Fundamentals In Cancer Medicine

New Era of Personalized Medicine

Targeting Drugs For Each Unique Genetic Profile

BY ROBERT LANGRETH And MICHAEL WALDHOLZ

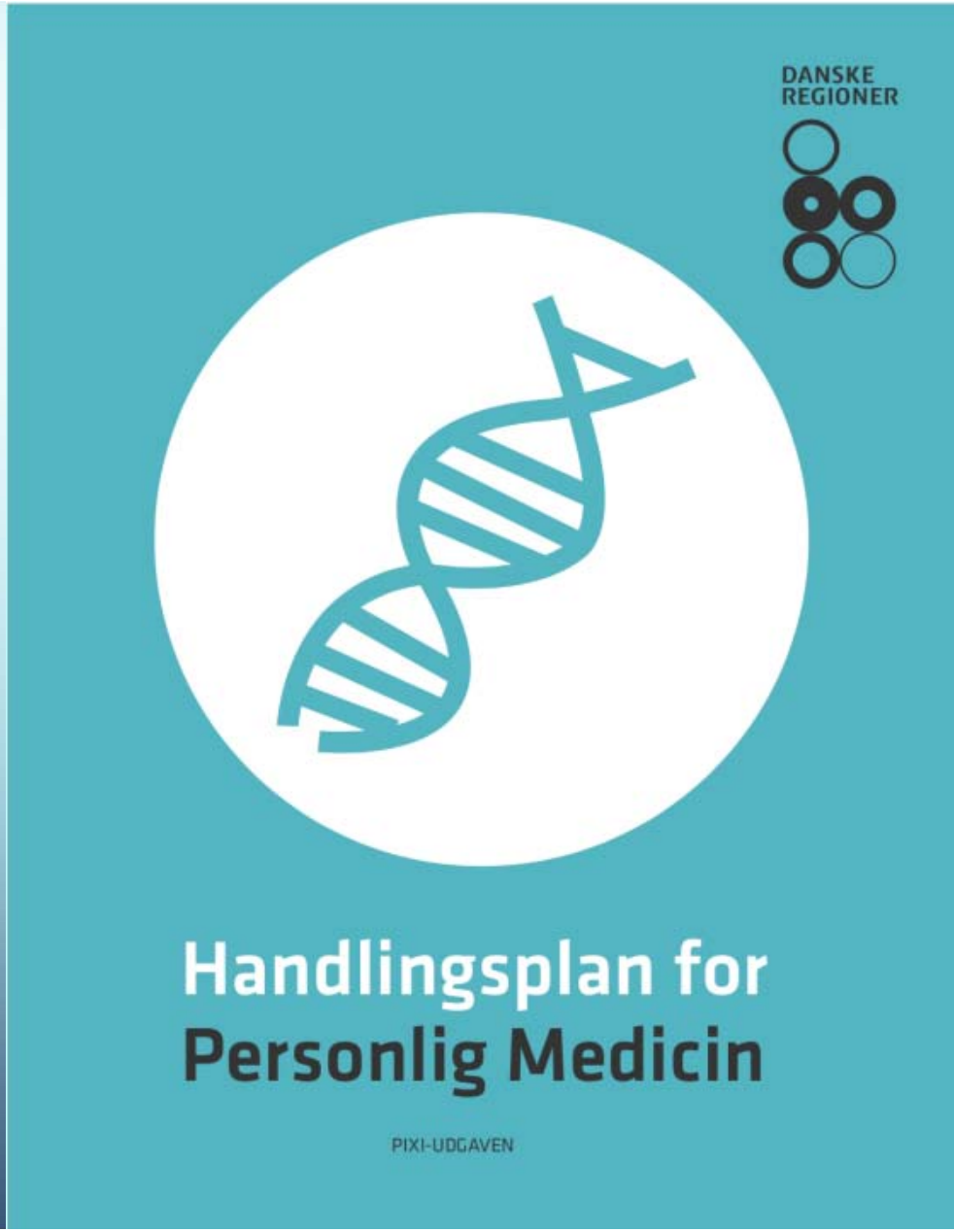
Staff Reporters of THE WALL STREET JOURNAL

"One will be able to pull a CD out of one´s pocket and say: "Here is a human being: it´s me".

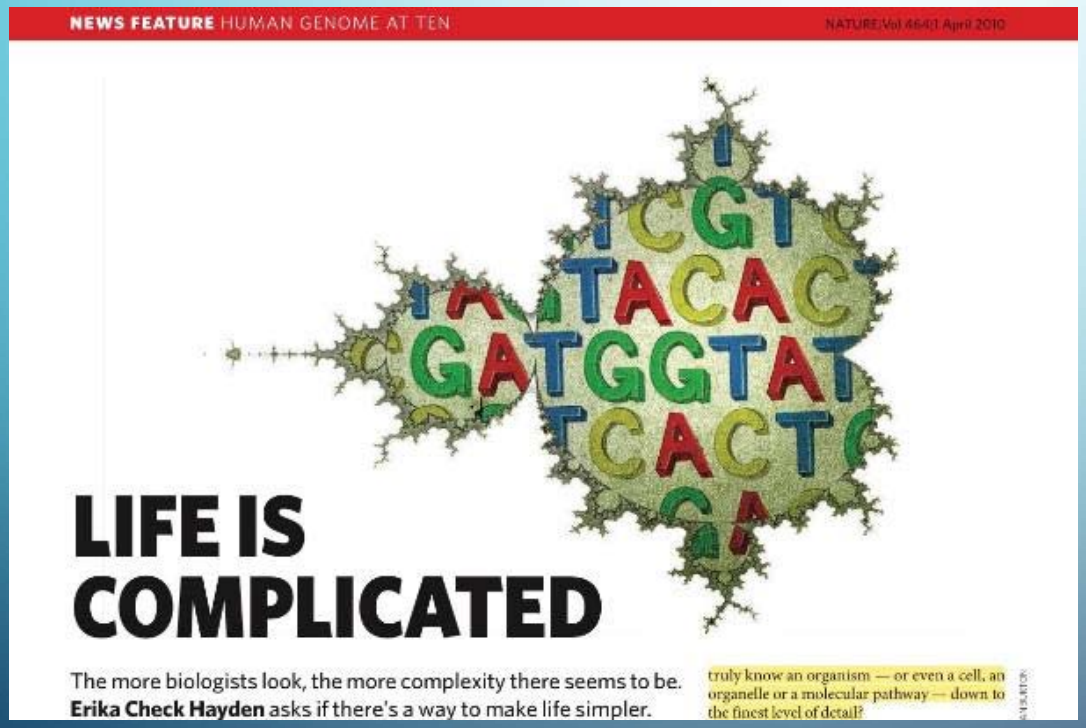
Walter Gilbert 1992

THE VISION (DANISH VERSION, 2015)

«Den stigende indsigt i generne vil reformere den måde vi tænker sygdom på hele diagnostikken, samt behandling og forebyggelse. Billig og hurtig DNA-sekventering vil i de kommende årtier medfører helt nye former for individualiseret behandling og livslang forebyggelse».

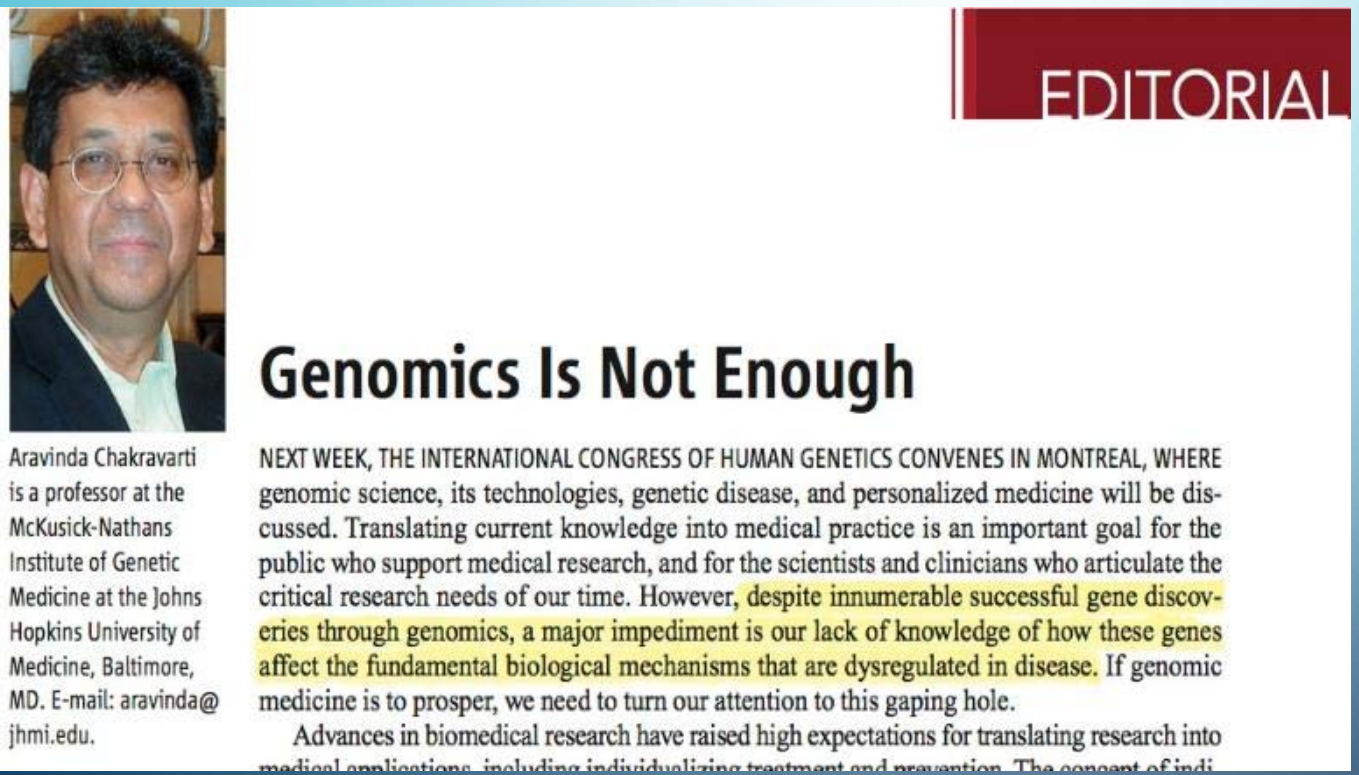


PERSONALIZED/PRECISION MEDICINE



Nature Ed.(2010) "Has human health truly benefited from the sequencing of the human genome? (…) 'not much'."

PERSONALIZED MEDICINE



Aravinda Chakravarti is a professor at the McKusick-Nathans Institute of Genetic Medicine at the Johns Hopkins University of Medicine, Baltimore, MD. E-mail: aravinda@jhmi.edu.

EDITORIAL

Genomics Is Not Enough

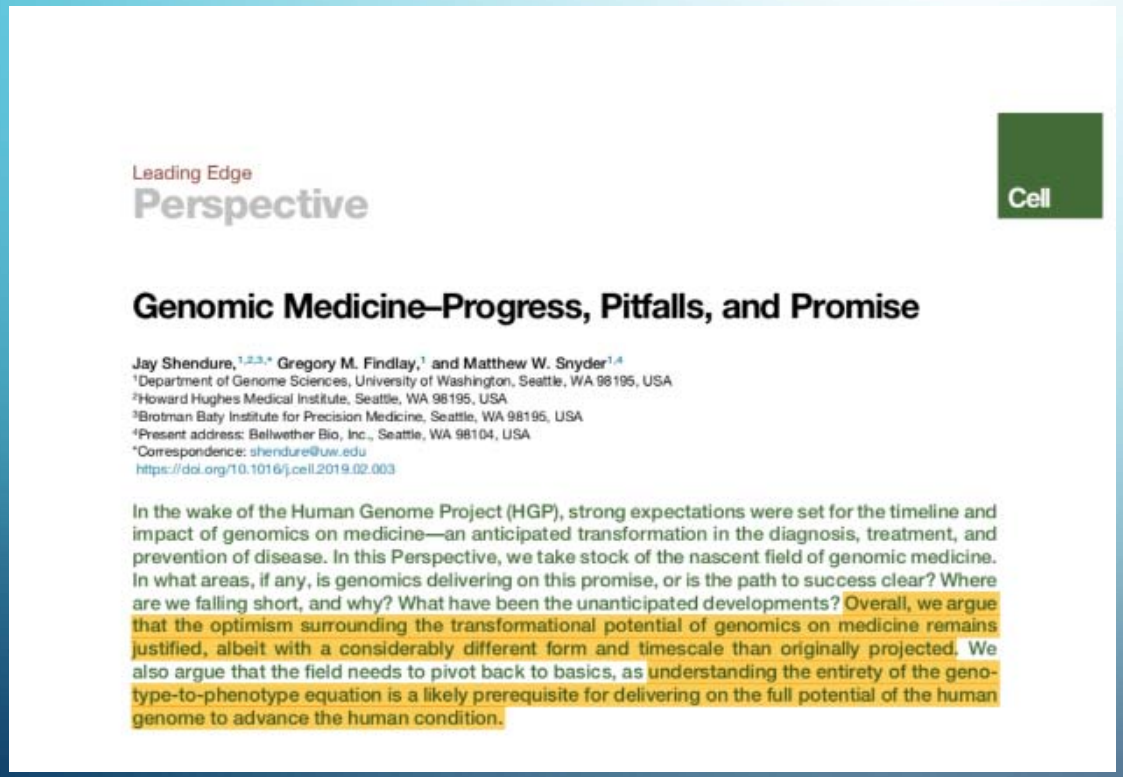
NEXT WEEK, THE INTERNATIONAL CONGRESS OF HUMAN GENETICS CONVENES IN MONTREAL, WHERE genomic science, its technologies, genetic disease, and personalized medicine will be discussed. Translating current knowledge into medical practice is an important goal for the public who support medical research, and for the scientists and clinicians who articulate the critical research needs of our time. However, despite innumerable successful gene discoveries through genomics, a major impediment is our lack of knowledge of how these genes affect the fundamental biological mechanisms that are dysregulated in disease. If genomic medicine is to prosper, we need to turn our attention to this gaping hole.

Advances in biomedical research have raised high expectations for translating research into

"The lessons from genome biology are quite clear. Genes and their products almost never act alone, but in networks"

Science Editorial 2011

PERSONALIZED MEDICINE



Leading Edge

Perspective

Cell

Genomic Medicine–Progress, Pitfalls, and Promise

Jay Shendure,[1,2,3,*] Gregory M. Findlay,[1] and Matthew W. Snyder[1,4]
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https://doi.org/10.1016/j.cell.2019.02.003

In the wake of the Human Genome Project (HGP), strong expectations were set for the timeline and impact of genomics on medicine—an anticipated transformation in the diagnosis, treatment, and prevention of disease. In this Perspective, we take stock of the nascent field of genomic medicine. In what areas, if any, is genomics delivering on this promise, or is the path to success clear? Where are we falling short, and why? What have been the unanticipated developments? Overall, we argue that the optimism surrounding the transformational potential of genomics on medicine remains justified, albeit with a considerably different form and timescale than originally projected. We also argue that the field needs to pivot back to basics, as understanding the entirety of the genotype-to-phenotype equation is a likely prerequisite for delivering on the full potential of the human genome to advance the human condition.

«Understanding the entirety of the genotype-to-phenotype equation is a likely prerequisite for delivering on the full potential of the human genome to advance the human condition».

- Shendure et al (2019)

PERSONALIZED MEDICINE AND «BIG DATA»

Leading Edge

a new era of data-driven medicine

e the assessment and management of

advances that enable the assessment and management of human health at an unprecedented level of resolution—what we refer to as high-definition medicine. Our ability to assess human health in high definition is enabled, in part, by advances in DNA sequencing, physiological and environmental monitoring, advanced imaging, and behavioral tracking. Our ability to understand and act upon these observations at equally high precision is driven by advances in genome editing, cellular reprogramming, tissue engineering, and information technologies, especially artificial intelligence. In this review, we will examine the core disciplines that enable high-definition medicine and project how these technologies will alter the future of medicine.

Wearables

Is Chris Dancy the Most Quantified Self in America?

By Ira Boudway June 05, 2014

PERSONALIZED MEDICINE

Genome

↓

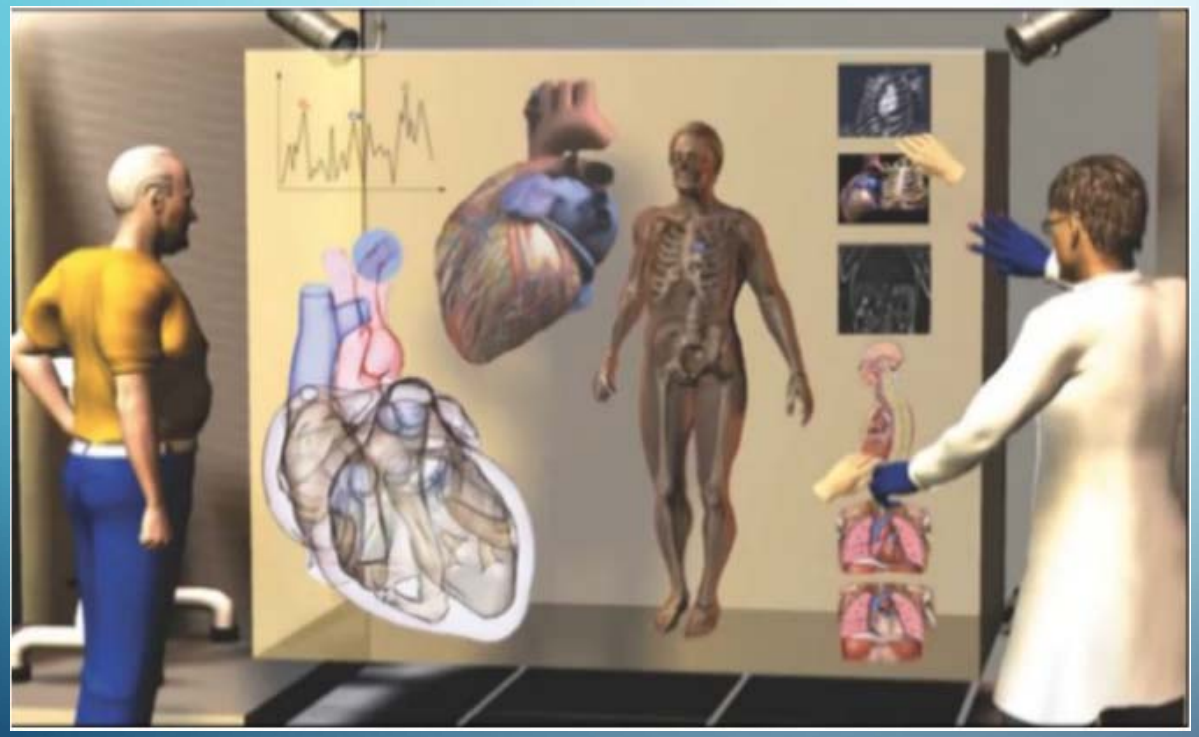
Genome
X
Phenome/
environome

PERSONALIZED MEDICINE

Screening genome

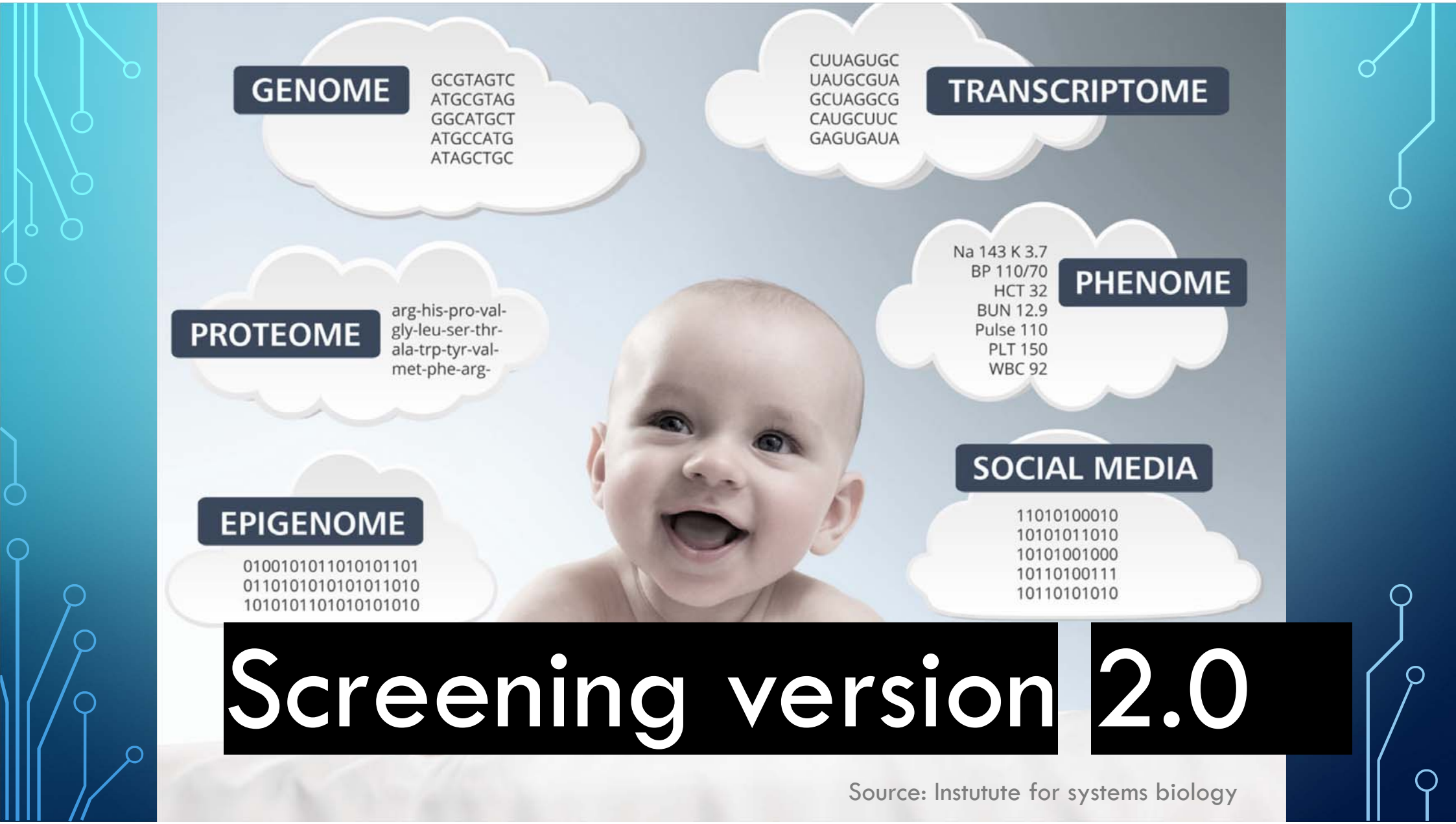
Screening the whole person - throughout life

«THE TRANSPARENT BODY»



- Avatar

- The digital patient



Screening version 2.0

Source: Instutute for systems biology

A promise of a revolution in individualized disease prevention/screening

Is this promise credible?

THE PREMISE FOR A REVOLUTION

Since «screening 2.0» will entail considerable harms and costs, personalized disease prevention must entail considerable benefit…

…in a relatively healthy population.

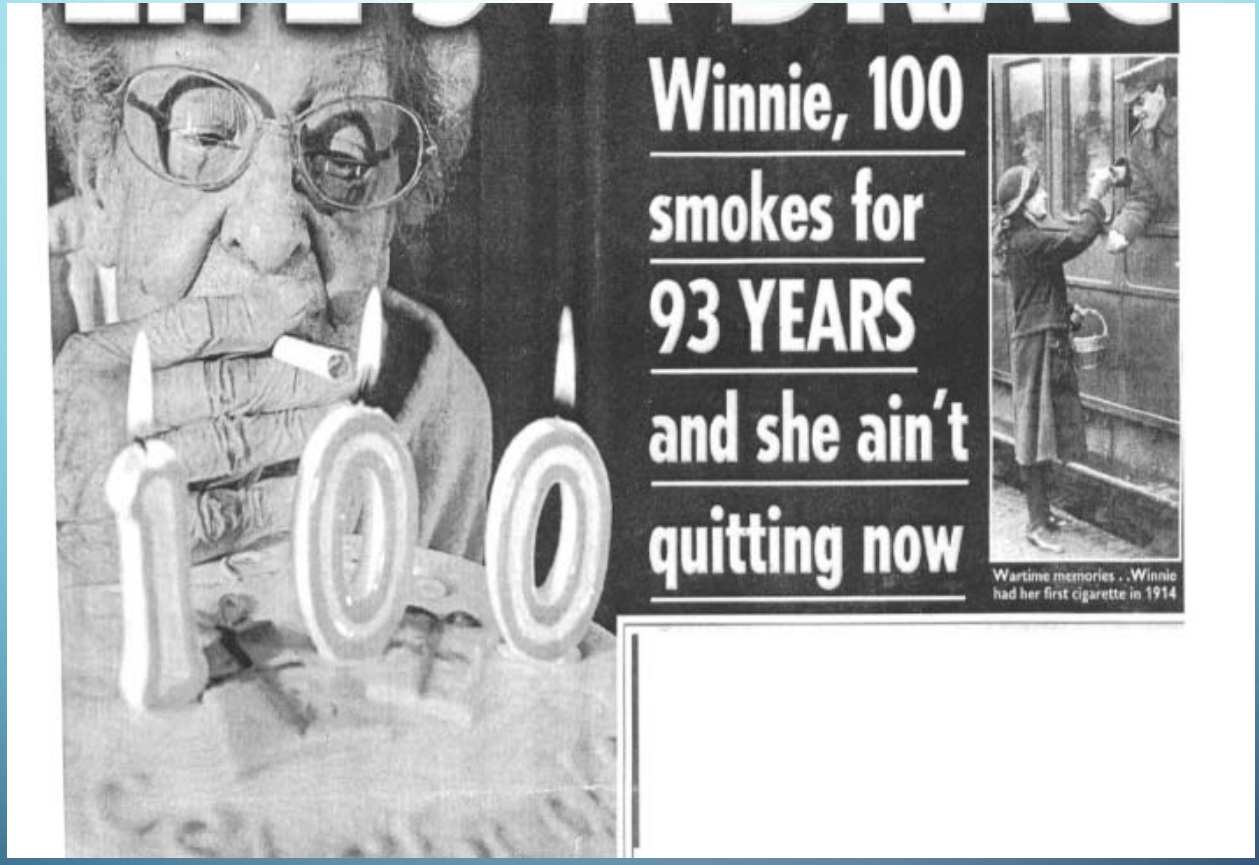
Problems of prediction and control in complex biological systems

PROBLEMS OF PREDICTABILITY

‘The complexity of control, overlaid by the unique experience of each individual, means that we must continue to treat every human as unique and special, and not imagine that we can predict the course of a human life other than in broad terms’

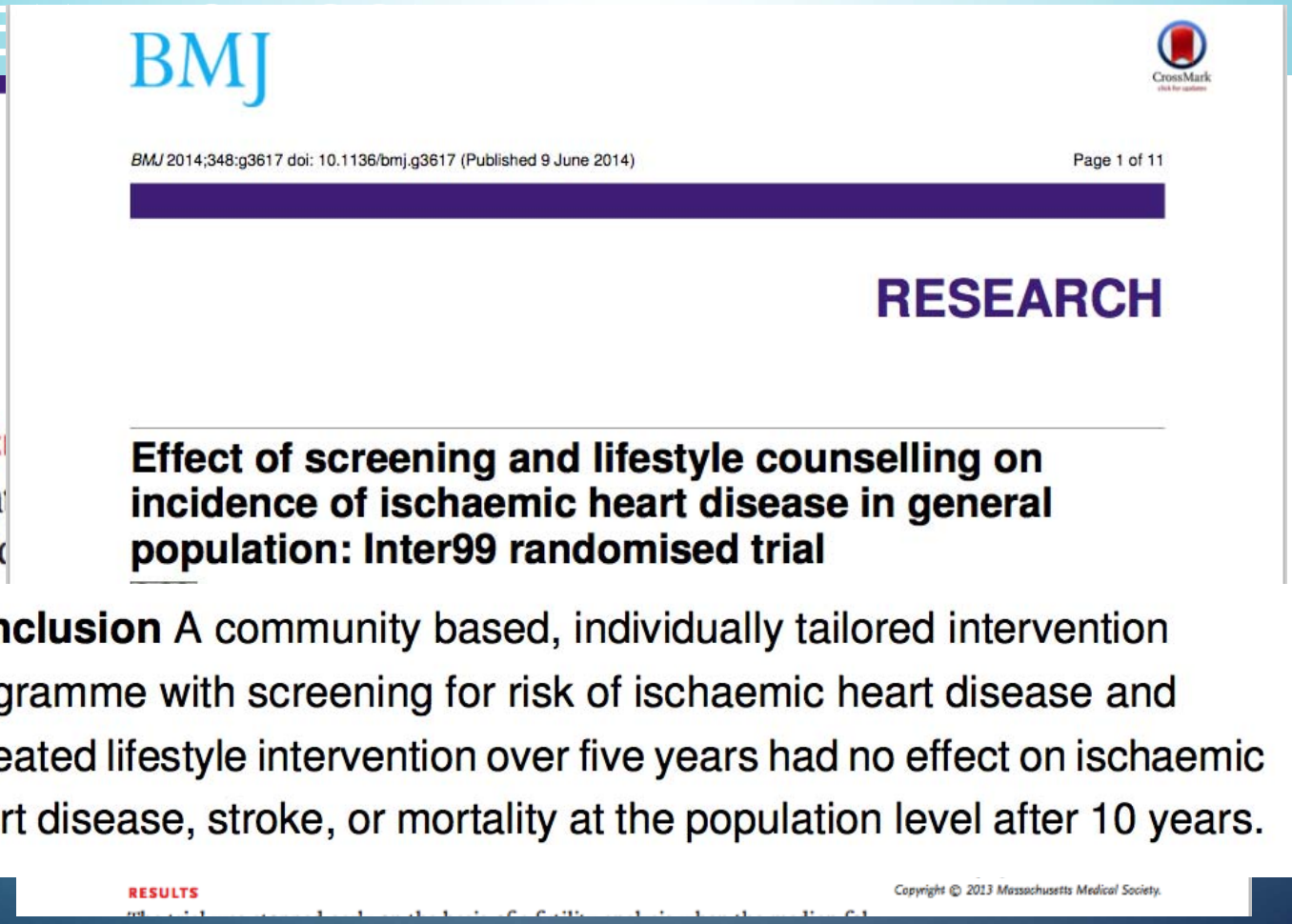
- John Sulston, A common thread, 2002

UNPREDICTABILITY: GOOD LUCK, BAD LUCK



Ref: Epidemiology, epigenetics and the 'Gloomy Prospect': embracing randomness in population health research and practice (Smith, G.D 2011).

PROBLE



BMJ

BMJ 2014;348:g3617 doi: 10.1136/bmj.g3617 (Published 9 June 2014)

RESEARCH

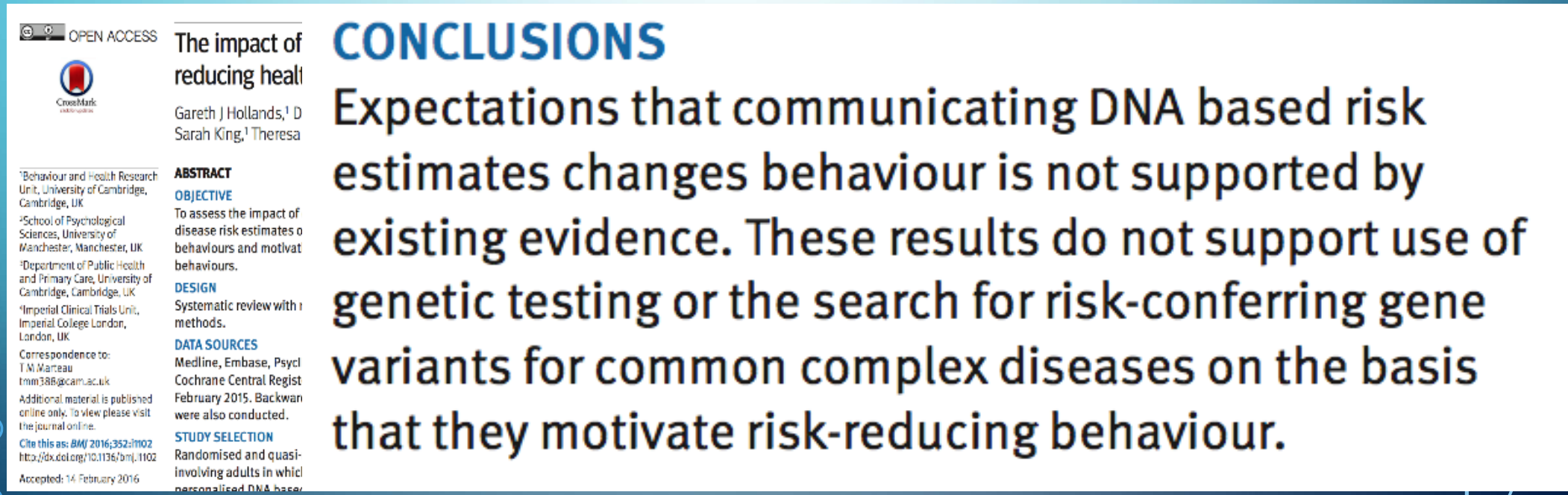
CONC
An in
cardi

Effect of screening and lifestyle counselling on incidence of ischaemic heart disease in general population: Inter99 randomised trial

Conclusion A community based, individually tailored intervention programme with screening for risk of ischaemic heart disease and repeated lifestyle intervention over five years had no effect on ischaemic heart disease, stroke, or mortality at the population level after 10 years.

RESULTS

PROBLEMS OF CONTROLLABILITY



OPEN ACCESS

The impact of
reducing healt

Gareth J Hollands,[1] D
Sarah King,[1] Theresa

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Additional material is published online only. To view please visit the journal online.

Cite this as: BMJ 2016;352:i1102
http://dx.doi.org/10.1136/bmj.i1102

Accepted: 14 February 2016

ABSTRACT

OBJECTIVE
To assess the impact of disease risk estimates o behaviours and motivat behaviours.

DESIGN
Systematic review with methods.

DATA SOURCES
Medline, Embase, Psycl Cochrane Central Regist February 2015. Backwar were also conducted.

STUDY SELECTION
Randomised and quasi- involving adults in whic

CONCLUSIONS

Expectations that communicating DNA based risk estimates changes behaviour is not supported by existing evidence. These results do not support use of genetic testing or the search for risk-conferring gene variants for common complex diseases on the basis that they motivate risk-reducing behaviour.

PROBLEMS OF CONTROLLABILITY

Research

JAMA | Original Investigation

Effect of Wearable Technology Combin
Intervention on Long-term Weight Loss
The IDEA Randomized Clinical Trial

John M. Jakicic, PhD; Kelliann K. Davis, PhD; Renee J. Rogers, PhD; Wendy C. King, PhD; Marsha
Diane Helsel, PhD, RD; Amy D. Rickman, PhD, RD, LDN; Abdus S. Wahed, PhD; Steven H. Belle, P

IMPORTANCE Effective long-term treatments are needed to address the obesity e
Numerous wearable technologies specific to physical activity and diet are available
unclear if these are effective at improving weight loss.

OBJECTIVE To test the hypothesis that, compared with a standard behavioral weig
intervention (standard intervention), a technology-enhanced weight loss interven
(enhanced intervention) would result in greater weight loss.

DESIGN, SETTING, PARTICIPANTS Randomized clinical trial conducted at the Univer
Pittsburgh and enrolling 471 adult participants between October 2010 and Octobe
with data collection completed by December 2014.

INTERVENTIONS Participants were placed on a low-calorie diet, prescribed increas
physical activity, and had group counseling sessions. At 6 months, the interventio
telephone counseling sessions, text message prompts, and access to study materi
website. At 6 months, participants randomized to the standard intervention grou
self-monitoring of diet and physical activity using a website, and those randomize
enhanced intervention group were provided with a wearable device and accompa
interface to monitor diet and physical activity.

RESULTS Among the 471 participants randomized (body mass index [BMI], 25 to <40; age range, 18-35 years; 28.9% nonwhite; 77.2% women), 470 (233 in the standard intervention group, 237 in the enhanced intervention group) initiated the interventions as randomized, and 74.5% completed the study. Weight change at 24 months differed significantly by intervention group (difference, 2.4 kg [95% CI, 1.0-3.7]; $P = .002$). Both groups had significant improvements in body composition, fitness, physical activity, and diet, with no significant difference between groups.

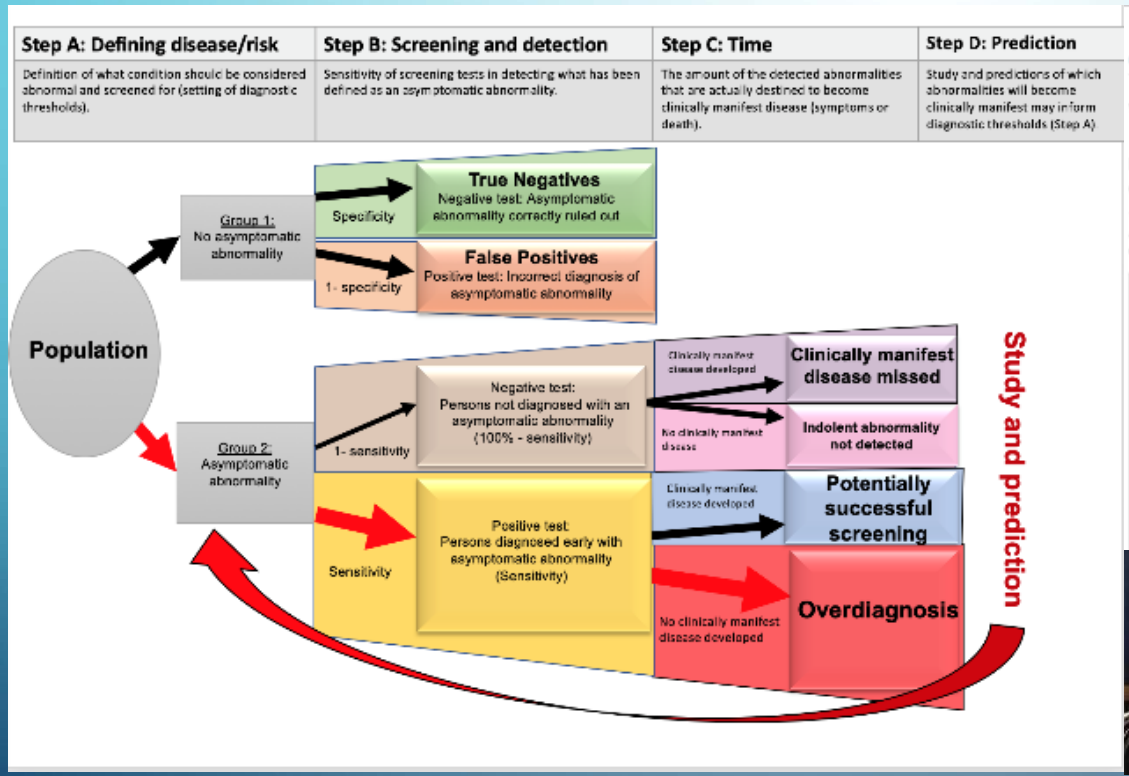
	Standard Intervention	Enhanced Intervention
Weight, mean (95% CI), kg		
Baseline	95.2 (93.0-97.3)	96.3 (94.2-98.5)
24 mo	89.3 (87.1-91.5)	92.8 (90.6-95.0)
Estimated weight loss, mean (95% CI), kg	5.9 (5.0-6.8)	3.5 (2.6-4.5)

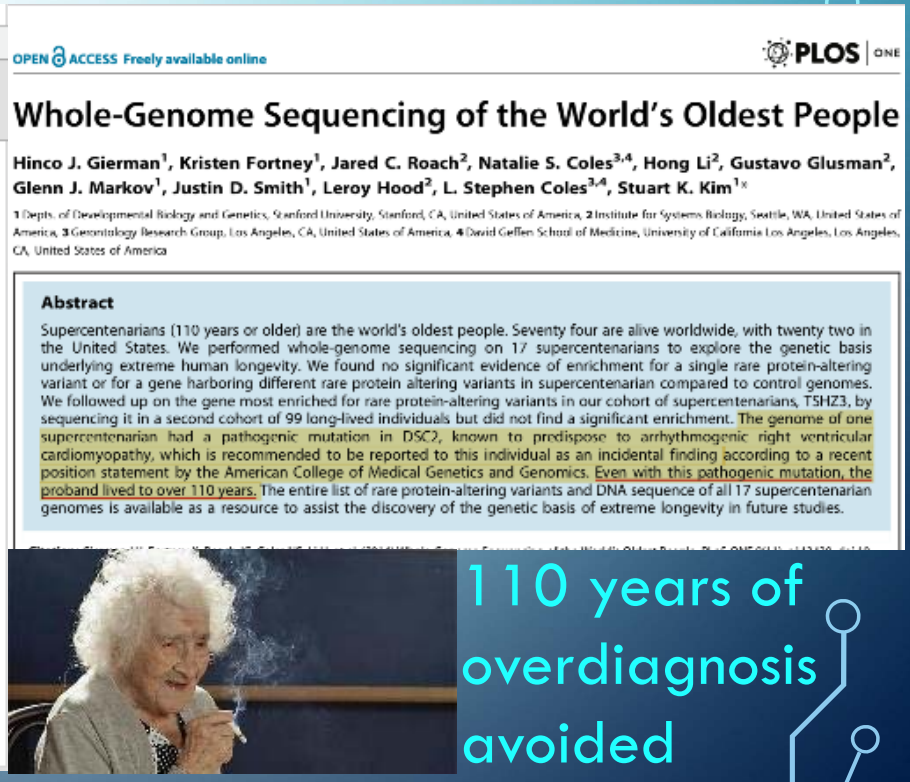
CONCLUSIONS AND RELEVANCE Among young adults with a BMI between 25 and less than 40, the addition of a wearable technology device to a standard behavioral intervention resulted in less weight loss over 24 months. Devices that monitor and provide feedback on physical activity may not offer an advantage over standard behavioral weight loss approaches.

What about overdiagnosis?

Can big data screening do good?

WHAT IS OVERDIAGNOSIS?





OPEN ACCESS Freely available online

PLOS ONE

Whole-Genome Sequencing of the World's Oldest People

Hinco J. Gierman[1], Kristen Fortney[1], Jared C. Roach[2], Natalie S. Coles[3,4], Hong Li[2], Gustavo Glusman[2], Glenn J. Markov[1], Justin D. Smith[1], Leroy Hood[2], L. Stephen Coles[3,4], Stuart K. Kim[1]*

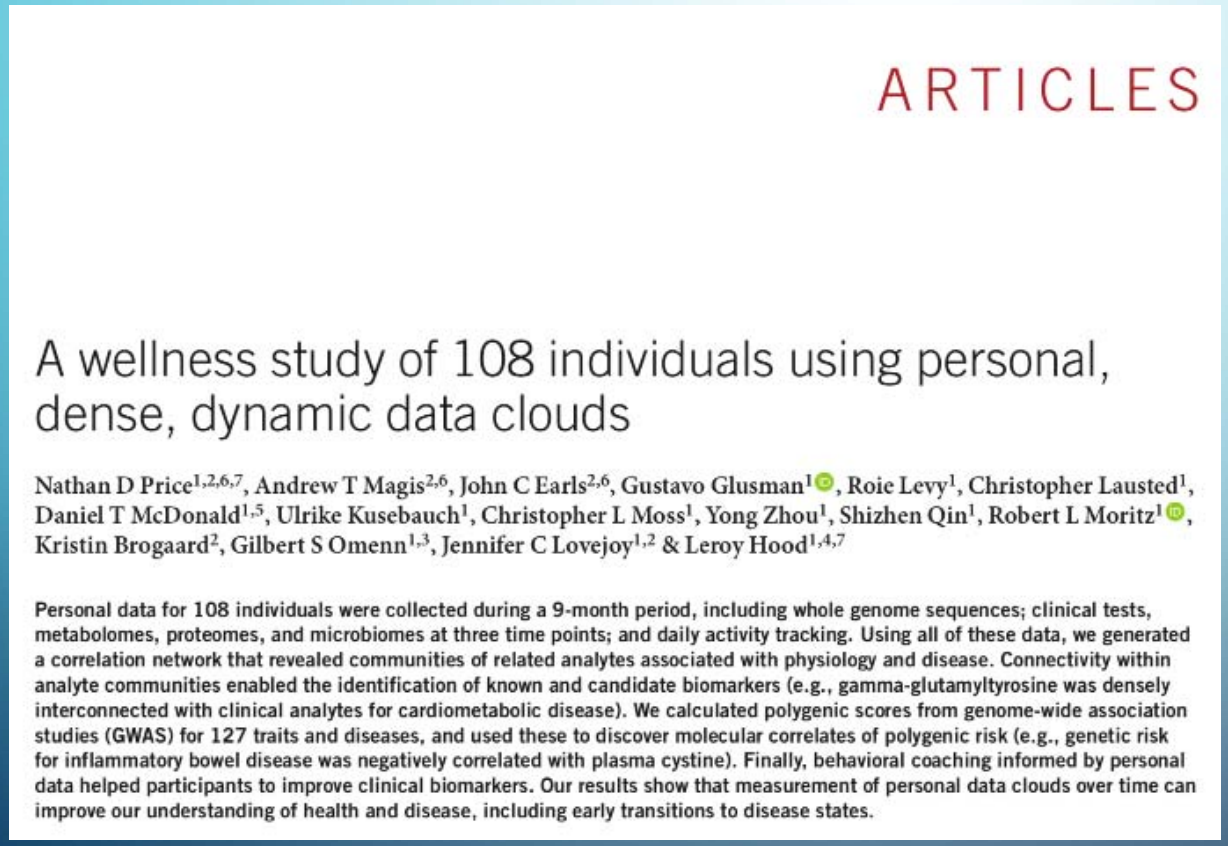
1 Depts. of Developmental Biology and Genetics, Stanford University, Stanford, CA, United States of America, 2 Institute for Systems Biology, Seattle, WA, United States of America, 3 Gerontology Research Group, Los Angeles, CA, United States of America, 4 David Geffen School of Medicine, University of California Los Angeles, Los Angeles, CA, United States of America

Abstract

Supercentenarians (110 years or older) are the world's oldest people. Seventy four are alive worldwide, with twenty two in the United States. We performed whole-genome sequencing on 17 supercentenarians to explore the genetic basis underlying extreme human longevity. We found no significant evidence of enrichment for a single rare protein-altering variant or for a gene harboring different rare protein altering variants in supercentenarian compared to control genomes. We followed up on the gene most enriched for rare protein-altering variants in our cohort of supercentenarians, TSHZ3, by sequencing it in a second cohort of 99 long-lived individuals but did not find a significant enrichment. The genome of one supercentenarian had a pathogenic mutation in DSC2, known to predispose to arrhythmogenic right ventricular cardiomyopathy, which is recommended to be reported to this individual as an incidental finding according to a recent position statement by the American College of Medical Genetics and Genomics. Even with this pathogenic mutation, the proband lived to over 110 years. The entire list of rare protein-altering variants and DNA sequence of all 17 supercentenarian genomes is available as a resource to assist the discovery of the genetic basis of extreme longevity in future studies.

110 years of overdiagnosis avoided

PIONEER 100 WELLNESS PROJECT



ARTICLES

A wellness study of 108 individuals using personal, dense, dynamic data clouds

Nathan D Price[1,2,6,7], Andrew T Magis[2,6], John C Earls[2,6], Gustavo Glusman[1], Roie Levy[1], Christopher Lausted[1], Daniel T McDonald[1,5], Ulrike Kusebauch[1], Christopher L Moss[1], Yong Zhou[1], Shizhen Qin[1], Robert L Moritz[1], Kristin Brogaard[2], Gilbert S Omenn[1,3], Jennifer C Lovejoy[1,2] & Leroy Hood[1,4,7]

Personal data for 108 individuals were collected during a 9-month period, including whole genome sequences; clinical tests, metabolomes, proteomes, and microbiomes at three time points; and daily activity tracking. Using all of these data, we generated a correlation network that revealed communities of related analytes associated with physiology and disease. Connectivity within analyte communities enabled the identification of known and candidate biomarkers (e.g., gamma-glutamyltyrosine was densely interconnected with clinical analytes for cardiometabolic disease). We calculated polygenic scores from genome-wide association studies (GWAS) for 127 traits and diseases, and used these to discover molecular correlates of polygenic risk (e.g., genetic risk for inflammatory bowel disease was negatively correlated with plasma cystine). Finally, behavioral coaching informed by personal data helped participants to improve clinical biomarkers. Our results show that measurement of personal data clouds over time can improve our understanding of health and disease, including early transitions to disease states.

- 9-month period
- whole genome sequencing (yielding 127 polygenic scores for disease risks
- three-times testing of metabolome (643 metabolites),
- proteome (262 proteins)
- microbiome (4616 taxonomic units),
- 218 other clinical tests
- activity tracking via “quantified self” technologies.

1) Price, N.D. *et al. Nat. Biotechnol.* **35**, *747–756* (2017).

2) See also Vogt, H., Green, S., Brodersen, J. *Nat. Biotechnol.* **36**, 8 (2018).

All 108 participants diagnosed with multiple «actionable possibilities» (risk factors)

CRAIG VENTER AND COLLEAGUES

PNAS

Precision medicine screening using whole-genome sequencing and advanced imaging to identify disease risk in adults

Bradley A. Perkins[a], C. Thomas Caskey[a,b,1], Pamila Brar[a], Eric Dec[a], David S. Karow[a,c], Andrew M. Kahn[a,d], Ying-Chen Claire Hou[a], Naisha Shah[a], Debbie Boeldt[a,e], Erin Coughlin[a], Gabby Hands[a], Victor Lavrenko[a], James Yu[a], Andrea Procko[a], Julia Appis[a], Anders M. Dale[f,g], Lining Guo[h], Thomas J. Jönsson[h], Bryan M. Wittmann[h], Istvan Bartha[a], Smriti Ramakrishnan[a], Axel Bernal[a], James B. Brewer[a,f], Suzanne Brewerton[a], William H. Biggs[a], Yaron Turpaz[a], and J. Craig Venter[a,i,1]

[a]Human Longevity, Inc., San Diego, CA 92121; [b]Molecular and Human Genetics, Baylor College of Medicine, Houston, TX 77030; [c]Department of Radiology, University of California, San Diego School of Medicine, San Diego, CA 92093; [d]Division of Cardiovascular Medicine, University of California, San Diego School

diseases associated with premature mortality. In addition to personal and family medical history and other clinical testing, we obtained whole-genome sequencing (WGS), noncontrast whole-body MRI, dual-energy X-ray absorptiometry (DXA), global metabolomics, a new blood test for prediabetes (Quantose IR), echocardiography (ECHO), ECG, and cardiac rhythm monitoring to identify age-related chronic disease risks. Precision medicine screening using WGS and advanced

Result: 164 of 209 (78%) diagnosed with disease or risk factors.[1]

1) Perkins et al (2018), Proceedings of the National Academy of Sciences

THE LATEST IN PRECISION MEDICINE

ARTICLES
https://doi.org/10.1038/s41591-019-0414-6
nature medicine

A longitudinal big data approach for precision health

Sophia Miryam Schüssler-Fiorenza Rose[1,2,3,16], Kévin Contrepois[1,16], Kegan J. Moneghetti[4,5,6], Wenyu Zhou[1], Tejaswini Mishra[1], Samson Mataraso[7,8], Orit Dagan-Rosenfeld[1], Ariel B. Ganz[1], Jessilyn Dunn[1,9], Daniel Hornburg[1], Shannon Rego[1], Dalia Perelman[1], Sara Ahadi[1], M. Reza Sailani[1], Yanjiao Zhou[10,11], Shana R. Leopold[10], Jieming Chen[12], Melanie Ashland[1], Jeffrey W. Christle[4,5], Monika Avina[1], Patricia Limcaoco[1], Camilo Ruiz[13], Marilyn Tan[14], Atul J. Butte[12], George M. Weinstock[10], George M. Slavich[15], Erica Sodergren[10], Tracey L. McLaughlin[14], Francois Haddad[4,5,*] and Michael P. Snyder[1,4,*]

Precision health relies on the ability to assess disease risk at an individual level, detect early preclinical conditions and initiate preventive strategies. Recent technological advances in omics and wearable monitoring enable deep molecular and physiological profiling and may provide important tools for precision health. We explored the ability of deep longitudinal profiling to make health-related discoveries, identify clinically relevant molecular pathways and affect behavior in a prospective longitudinal cohort (n = 109) enriched for risk of type 2 diabetes mellitus. The cohort underwent integrative personalized omics profiling from samples collected quarterly for up to 8 years (median, 2.8 years) using clinical measures and emerging technologies including genome, immunome, transcriptome, proteome, metabolome, microbiome and wearable monitoring. We discovered more than 67 clinically actionable health discoveries and identified multiple molecular pathways associated with metabolic, cardiovascular and oncologic pathophysiology. We developed prediction models for insulin resistance by using omics measurements, illustrating their potential to replace burdensome tests. Finally, study participation led the majority of participants to implement diet and exercise changes. Altogether, we conclude that deep longitudinal profiling can lead to actionable health discoveries and provide relevant information for precision health.

n=109 – (most healthy diabetes risk)

*Lab tests (quarterly) – many!

*"Deep molecular profiling"
Genome (n=88), immunome, transcriptome, proteome, metabolome, microbiome) (quarterly)

*Wearables/"exposome":
Continuous glucose monitoring (n=30)
Physiology/activity monitor (n=71

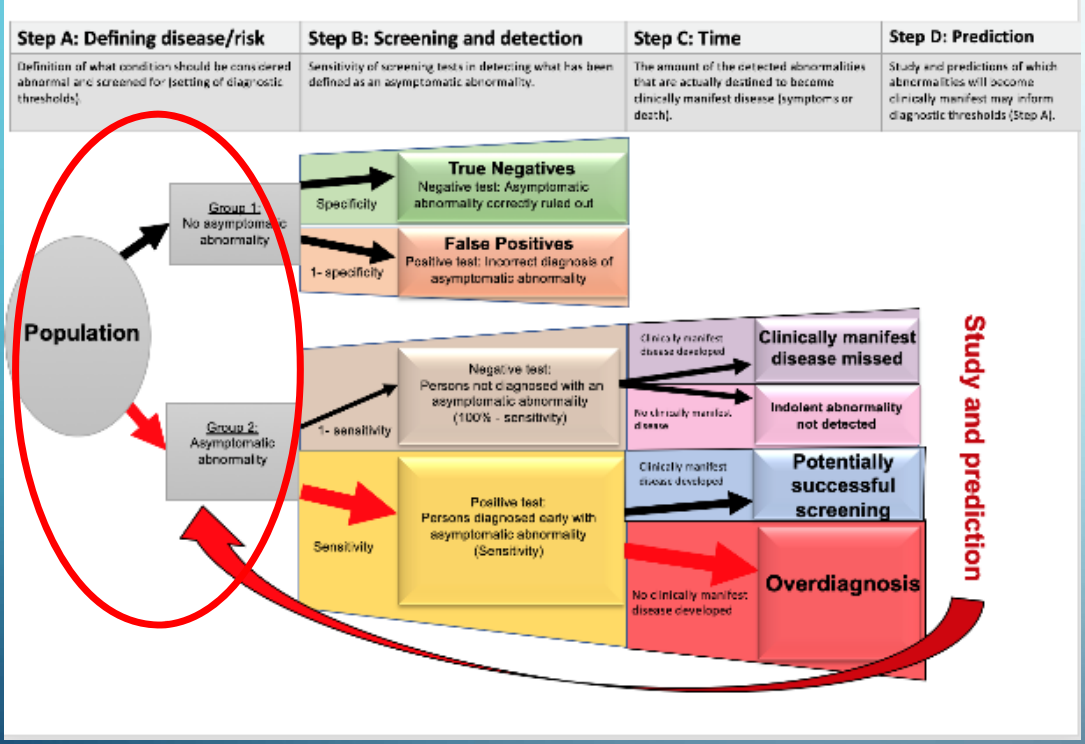
* Echocardiography, vascular ultrasound (n = 43, once)
*Cardiopulmonary max exercise (n = 36, once)

"THE NARCISSOME"

Result: 67 actionable findings in 109 people

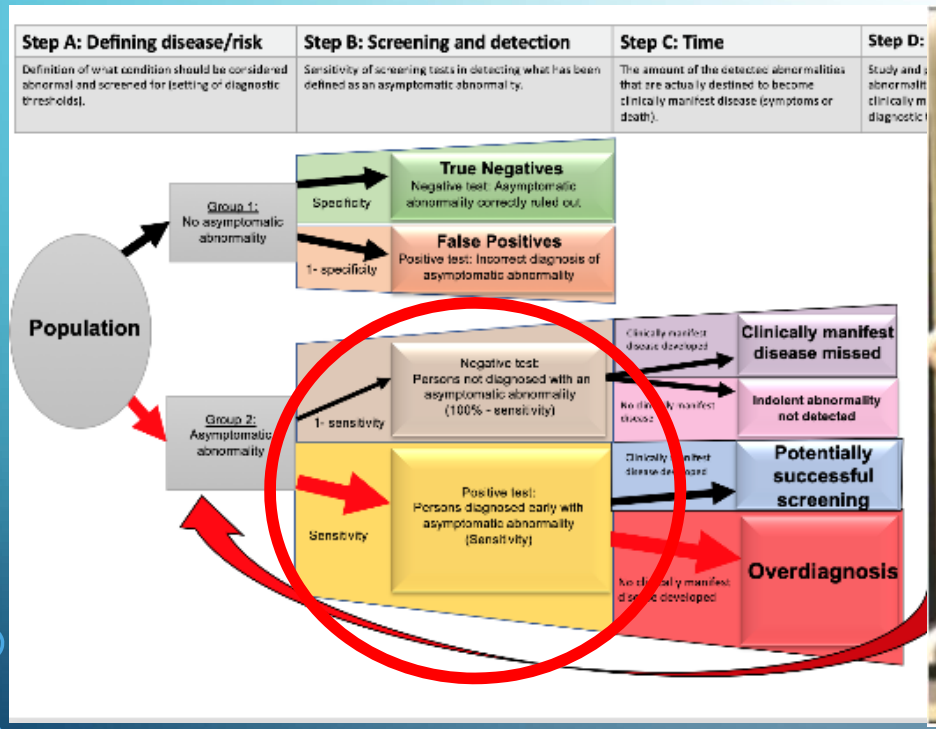
Likely substantial overdiagnosis

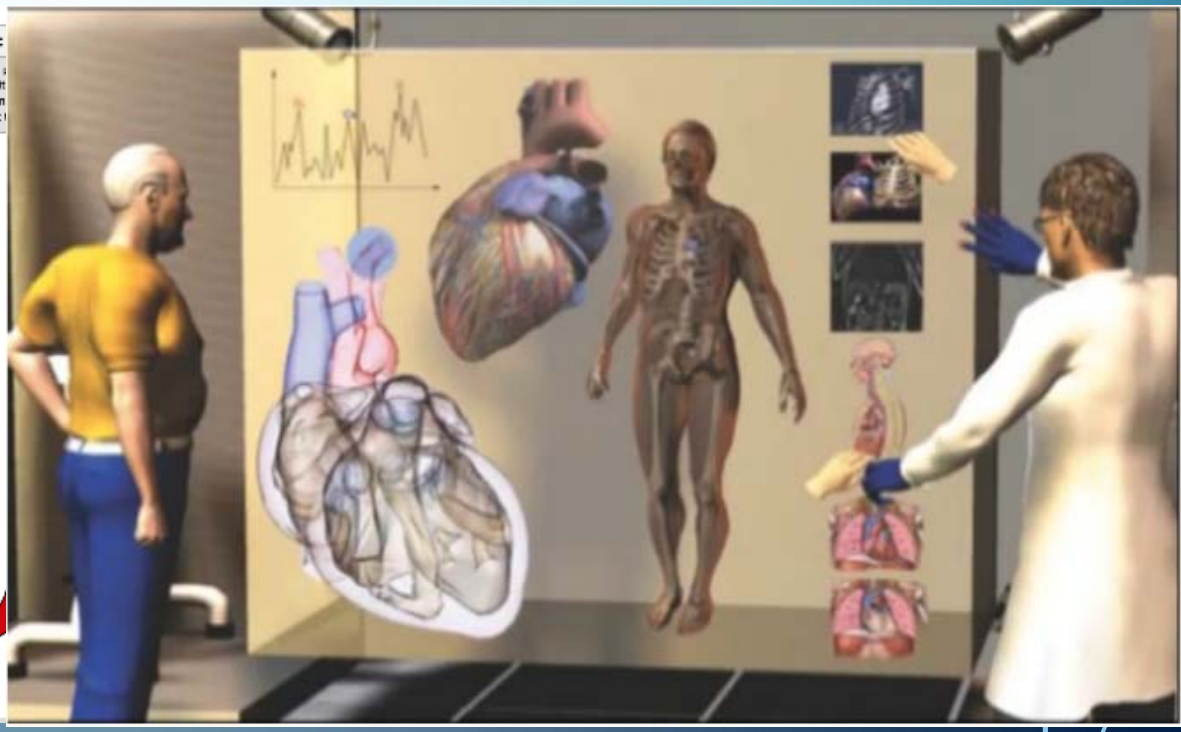
STEP A: LOW DIAGNOSTIC THRESHOLDS



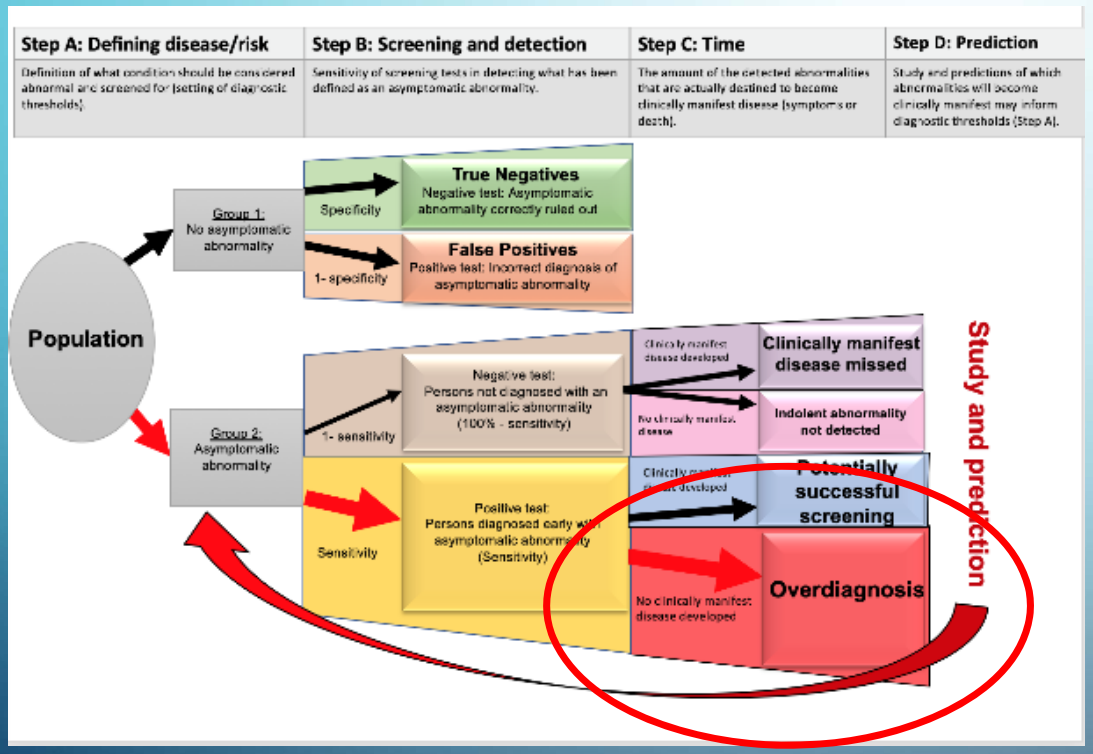
Pioneering precision medicine screening studies have used low diagnostic thresholds such as «prediabetes».

STEP B: THE DETECTION OF «EVERYTHING» ABNORMAL IN A «TRANSPARENT BODY»





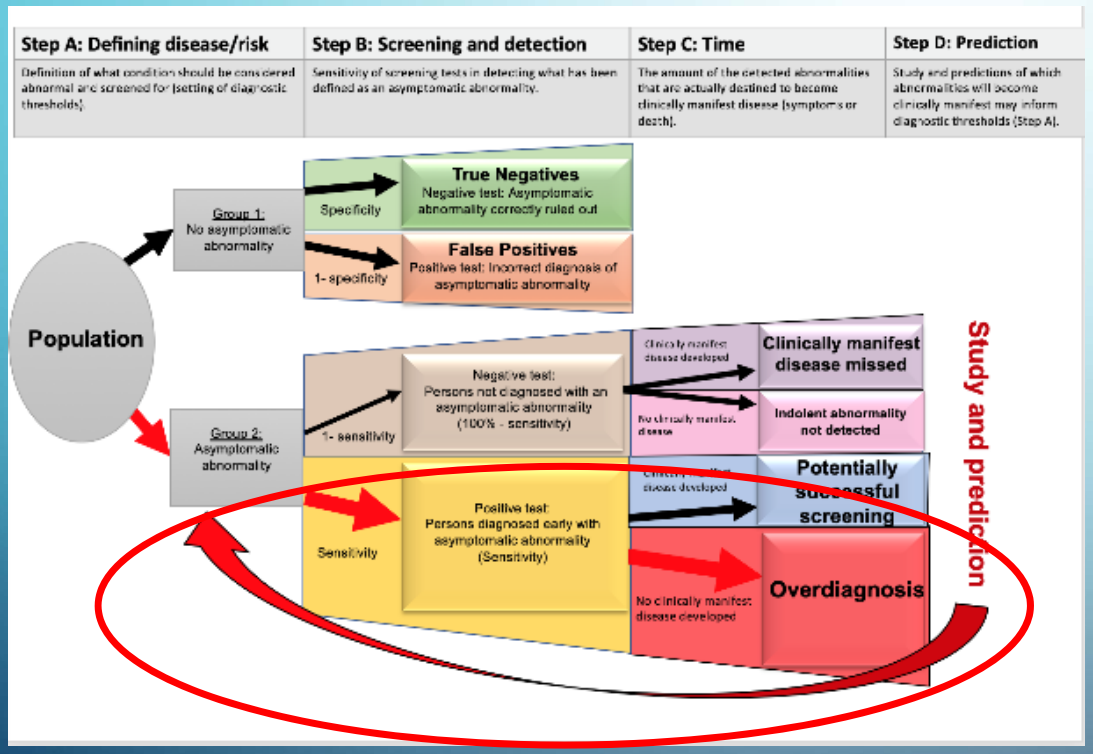
STEP C: DOES THE ABNORMALITY LEAD TO DISEASE?



-Screening for many abnormalities/diseases

- But only a few will lead to symptomatic disease

STEP D: PREDICTION OF WHAT WILL REALLY MATTER



The premise to avoid increased overdiagnosis:

1) To predict just which abnormalities will become clinically manifest.

2) And to «undiagnose» conditions previously labelled as dangerous

How far can we get in predicting just which abnormalites will become clinically manifest?

Complexity theory “has shown us that predictability is the exception rather than the rule, even for what seem like simple physical systems. A human being is immeasurably more complex than any demonstrably chaotic system – the question can be turned around: How can anything be predicted about a person?”

Physicist Colin Firth (BMJ)[1]

1) Chaos -predicting the unpredictable, Firth, WJ, BMJ, vol 303 (1991)

Precision medicine → imprecision medicine

«CARPET-BOMBING MEDICINE»

SCIENCE

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In This Doctor's Office, a Physical Exam Like No Other

Genetic and molecular analysis of 100 volunteers turned up hidden health problems in about half of them. Critics say the approach amounted to 'carpet-bombing' the body.

A colored scanning electron micrograph of human chromosomes. Dr. Michael Snyder of Stanford University believes that "deep profiles" of patients, including genetic sequencing, may provide early warning signs of disease. Stephen Ausmus/Science Source

By Carl Zimmer

May 9, 2019

To scientists like Michael Snyder, chair of the genetics department at Stanford University, the future of medicine is data — lots and lots of

"They carpet-bomb the body with tests and basically assume that the discovery of everything they hit is beneficial.
But there may be lots of collateral damage they don't consider».

"The approach is unlikely to work for people most in need — those who are poor, are barely hanging on, and have other things to worry about than monitoring themselves constantly".

CORRESPONDENCE

Precision medicine in the clouds

To the Editor: A billion-dollar question is whether precision medicine (also known as personalized, 'P4' or systems medicine) can substantially increase the utility of individualized disease prevention and population health[1,2]. In this respect, the first results from the Pioneer 100 Wellness Project (P100), featured in last August's issue, is a landmark[3,4]. The study sheds light on an approach that has primarily existed as a vision and precedes the US National Institutes of Health's (NIH; Bethesda, MD) All of Us study, which will include a million participants in a similar scheme (http://www.allofus.nih.gov/). The 100,000 participants in the 100K Wellness Project[3]. Against this background, we provide our view of whether the P100 study actually supports the prospect of substantial benefits from data-driven disease prevention and argue that it presents severe challenges.

The graphics of the correlational networks presented by Price *et al.*[3] do offer an interesting research potential for exploring connections in molecular networks and for identifying candidate biomarkers[3]. However, as yet there are only a few examples where such approaches have led to discoveries of therapeutic potential, especially when it comes utility. However, to measure an unbiased, valid effect in an *n*-of-1 randomized clinical trial, the study would have to include pairs of organized periods so that one period of each pair applies the experimental therapy and the other period applies usual care or placebo, and both the clinician and the patient have to be blinded[7]. In the P100 study, these strict methodological criteria do not apply. This makes it difficult to examine, for example, whether people alter their behavior in response to just being observed (the Hawthorne effect). Proponents of preventive precision medicine may argue that there are other ways of providing evidence for treatment efficacy as the number of measured variables increases and the number of research subjects that are similar enough for a personalized approach moves toward $n = 1$. This may involve continuous monitoring to observe significant changes in each particular person. The prospect of using such big data 'narratives' as evidence is intriguing. However, the P100 study fruitfully

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