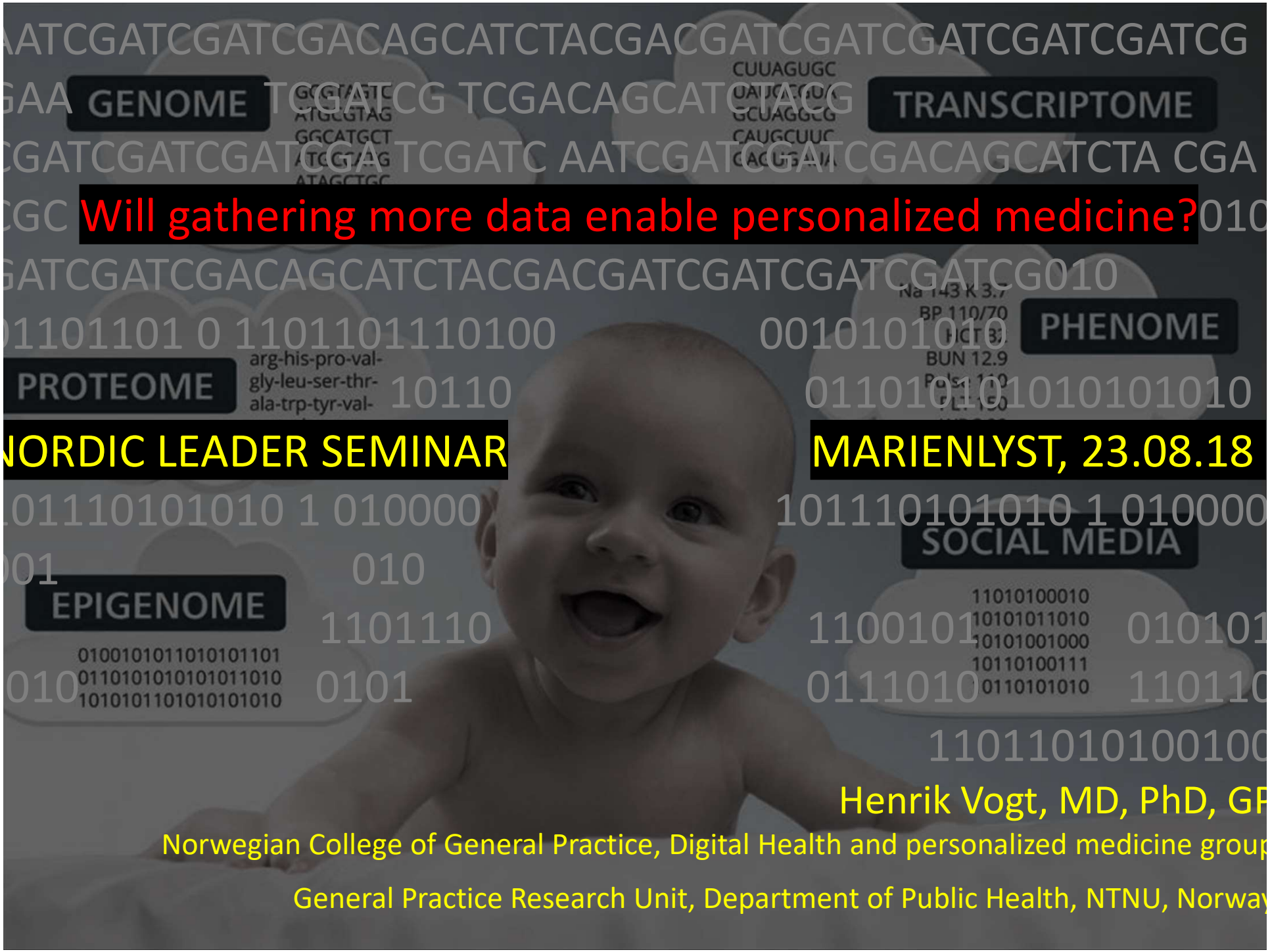

GENOME
TRANSCRIPTOME
PROTEOME
PHENOME
EPIGENOME
SOCIAL MEDIA
Will gathering more data enable personalized medicine?
NORDIC LEADER SEMINAR
MARIENLYST, 23.08.18
Henrik Vogt, MD, PhD, GP
Norwegian College of General Practice, Digital Health and personalized medicine group
General Practice Research Unit, Department of Public Health, NTNU, Norway

Show Markup Toolbar

Henrik Vogt

Systems Medicine as a Theoretical Framework for Primary Care Medicine

A Critical Analysis

Thesis for the Degree of Philosophiae Doctor

Trondheim, April 2017

Norwegian University of Science and Technology
Faculty of Medicine and Health Sciences
Department of Public Health and Nursing

NTNU
Norwegian University of
Science and Technology

PhD supervisors

Main supervisor
Prof. Linn Getz

Prof. Irene Hetlevik

Sara Green, ass prof

NTNU

DEN NORSKE
LEGEFORENING

Allmennmedisinsk
forskningsfond

Norwegian College of General Practice

“Personalized medicine”

Medicine that takes into account the precise characteristics of the individual in order to make practice more precise (tailored) and improved.

Personalized medicine

- “It is more important to know what sort of person has a disease than to know what sort of disease a person has.” [1]
- “If it were not for the great variability among individuals, medicine might as well be a science and not an art.”[2]

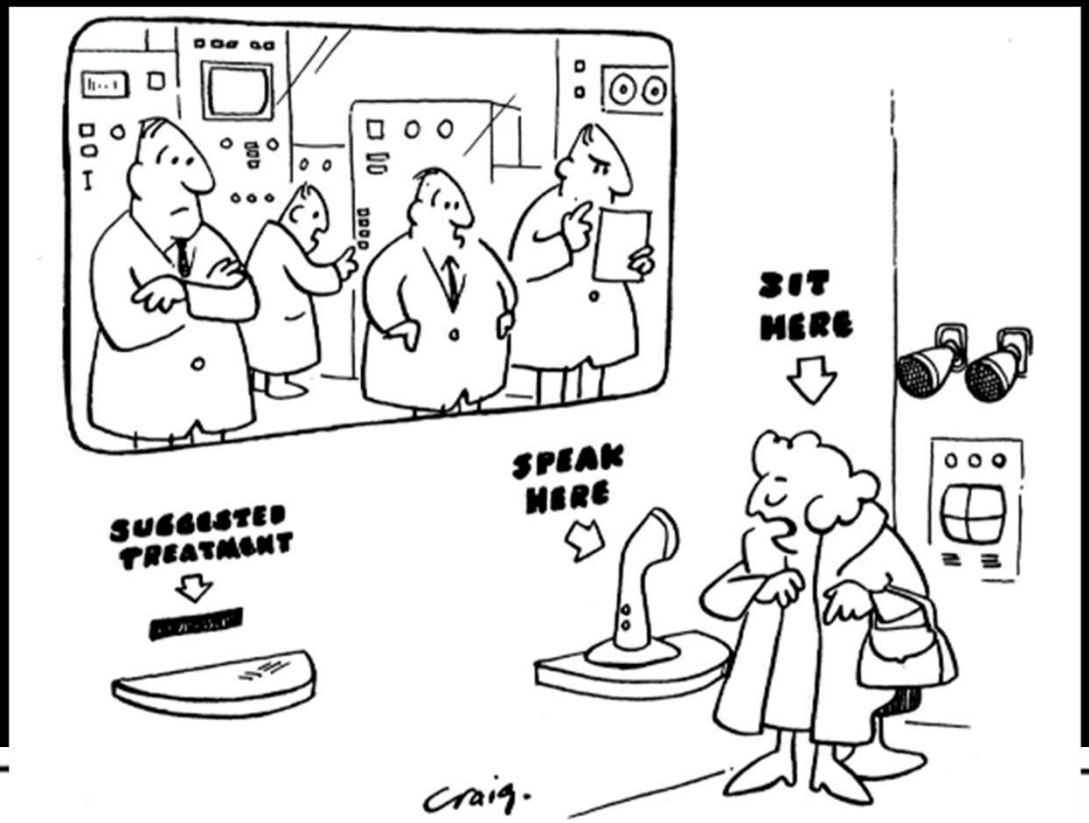
William Osler (1849-1919)

1) Stange, K.C (2009) 2) Tutton, R. (2012)

“Personalized medicine”

The Doctor by Luke Fields (1890)

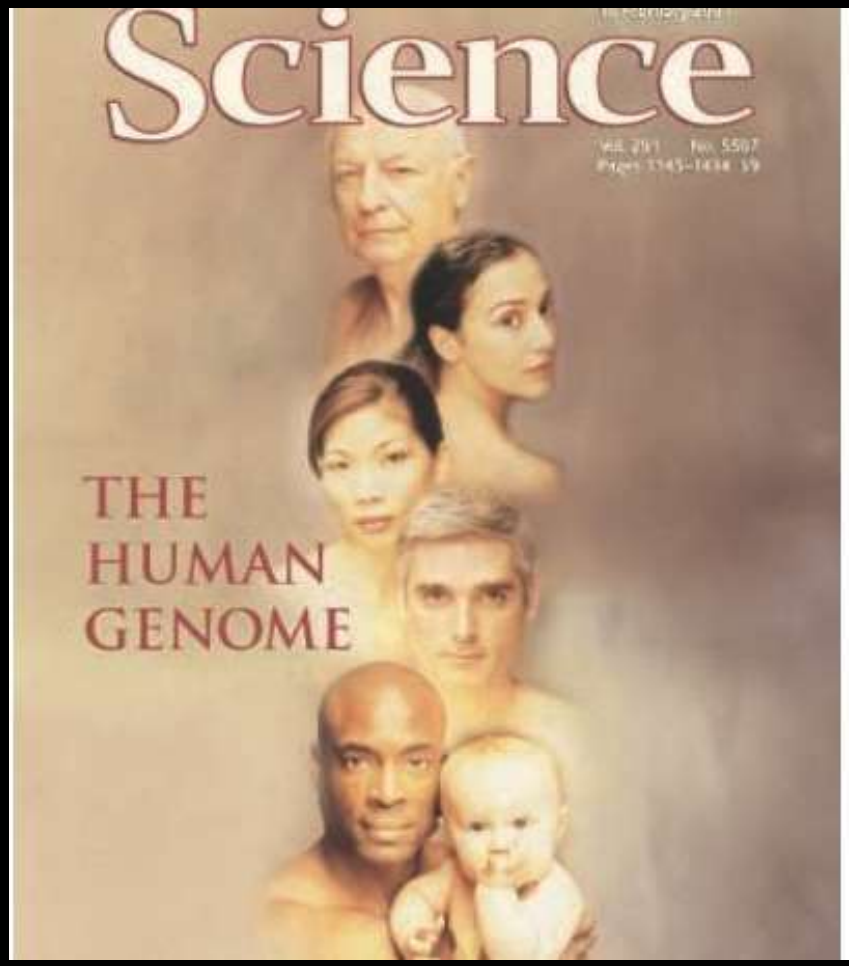
Personalized medicine

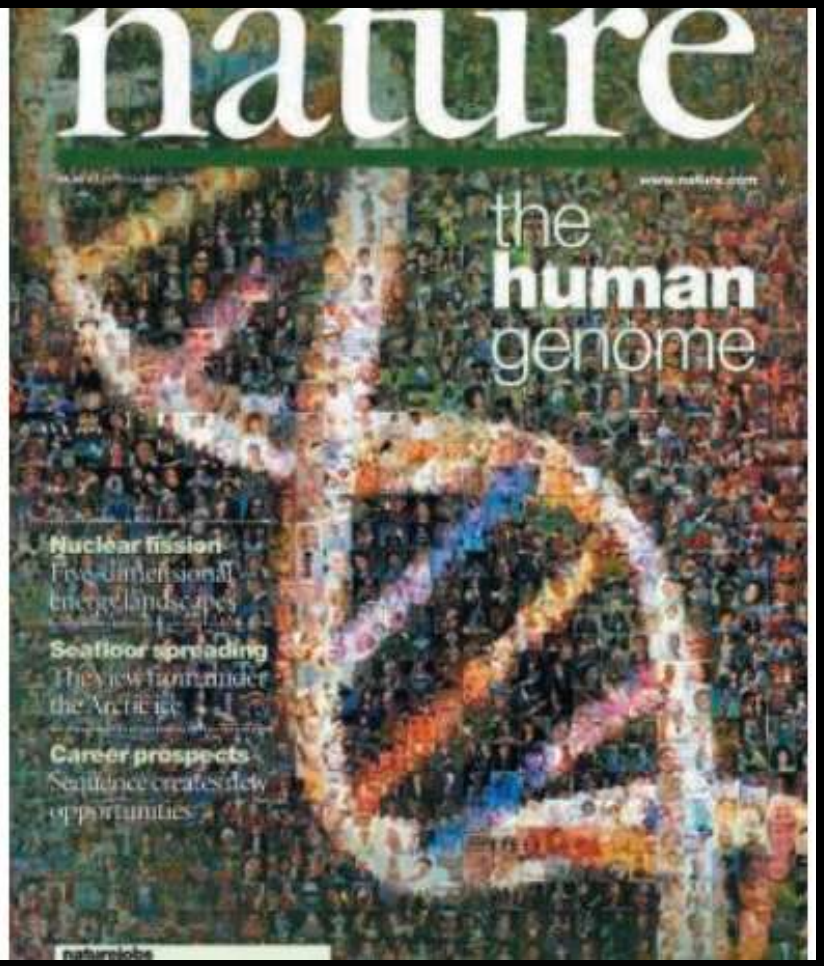


Can Personalized Medicine Survive?

by W. M. GIBSON, MB, ChB

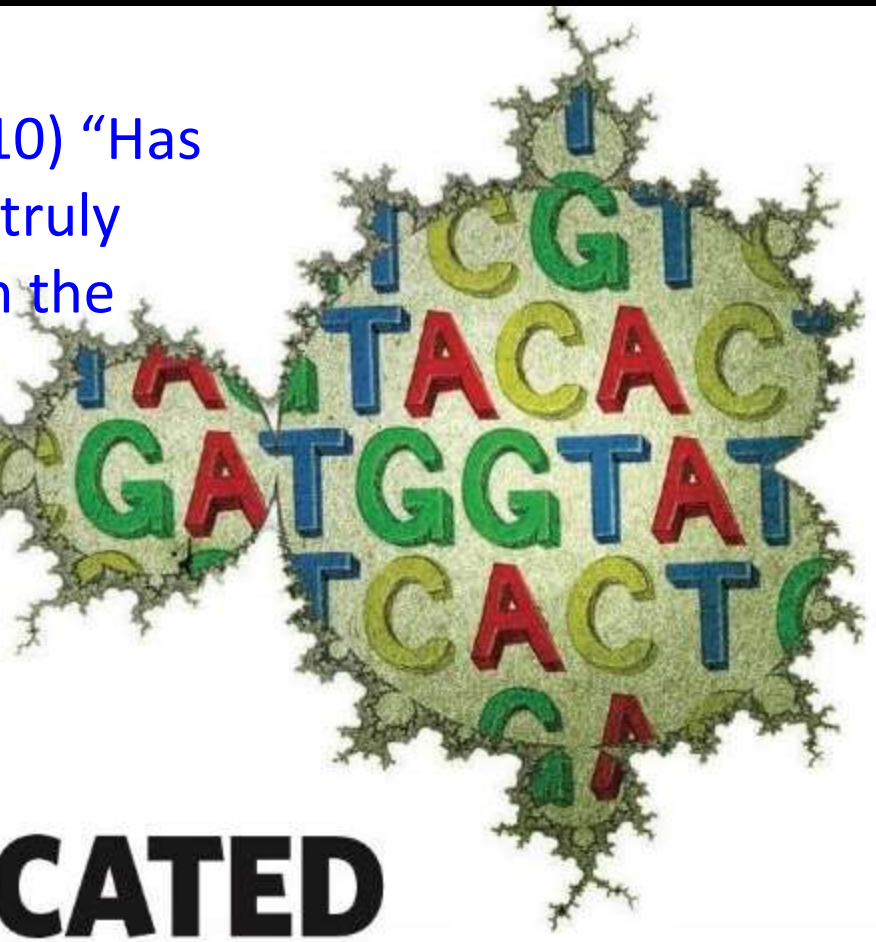
Personalized medicine





Personalized medicine

Nature Ed.(2010) “Has human health truly benefited from the sequencing of the human genome? (…) ‘not much’.”



LIFE IS COMPLICATED

Personalized medicine

"The lessons from genome biology are quite clear. Genes and their products almost never act alone, but in networks" – Science Editorial 2011

EDITORIAL

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.

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

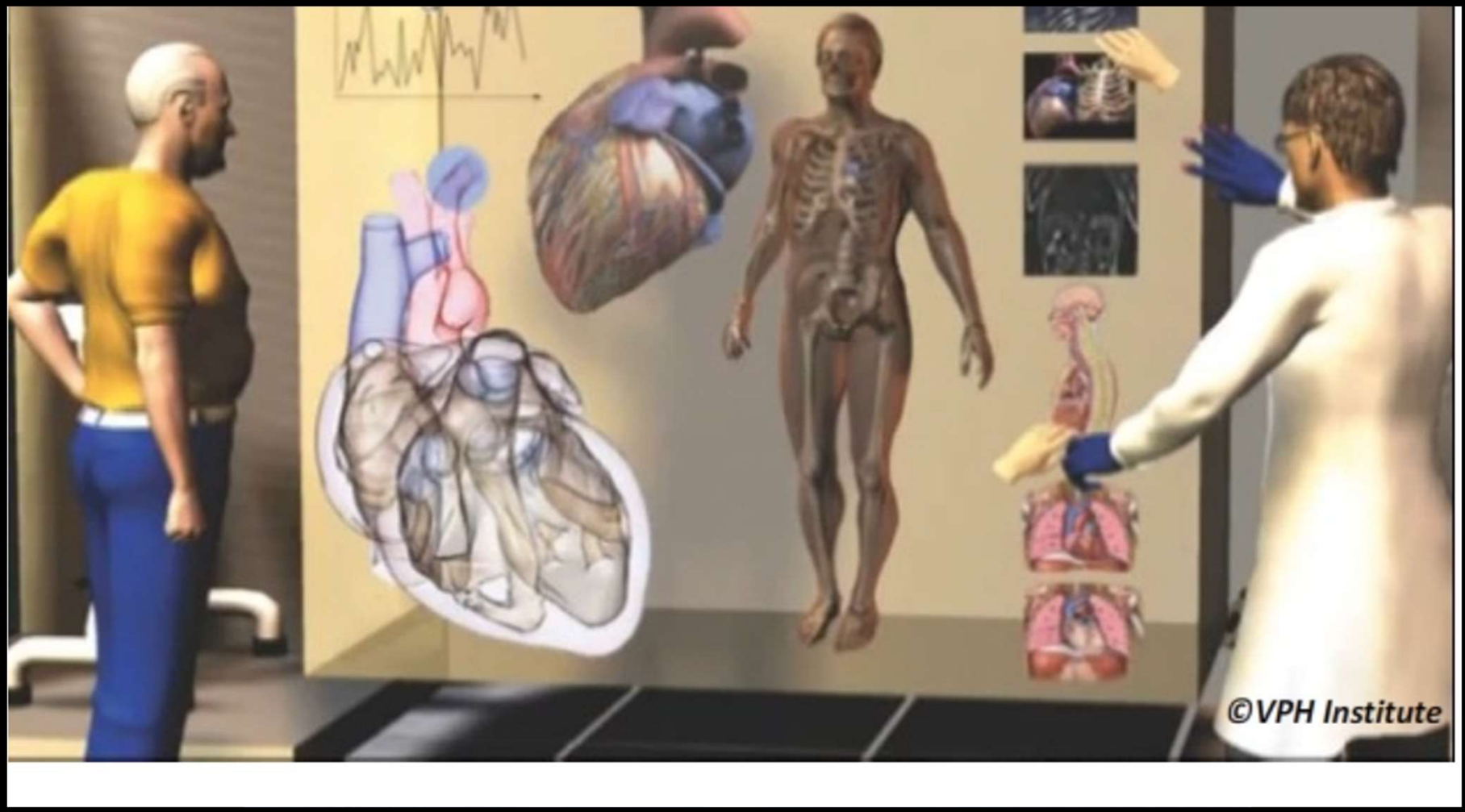
What is «big data»?

Wearables

Is Chris Dancy the Most Quantified Self in America?

By Ira Boudway June 05, 2014

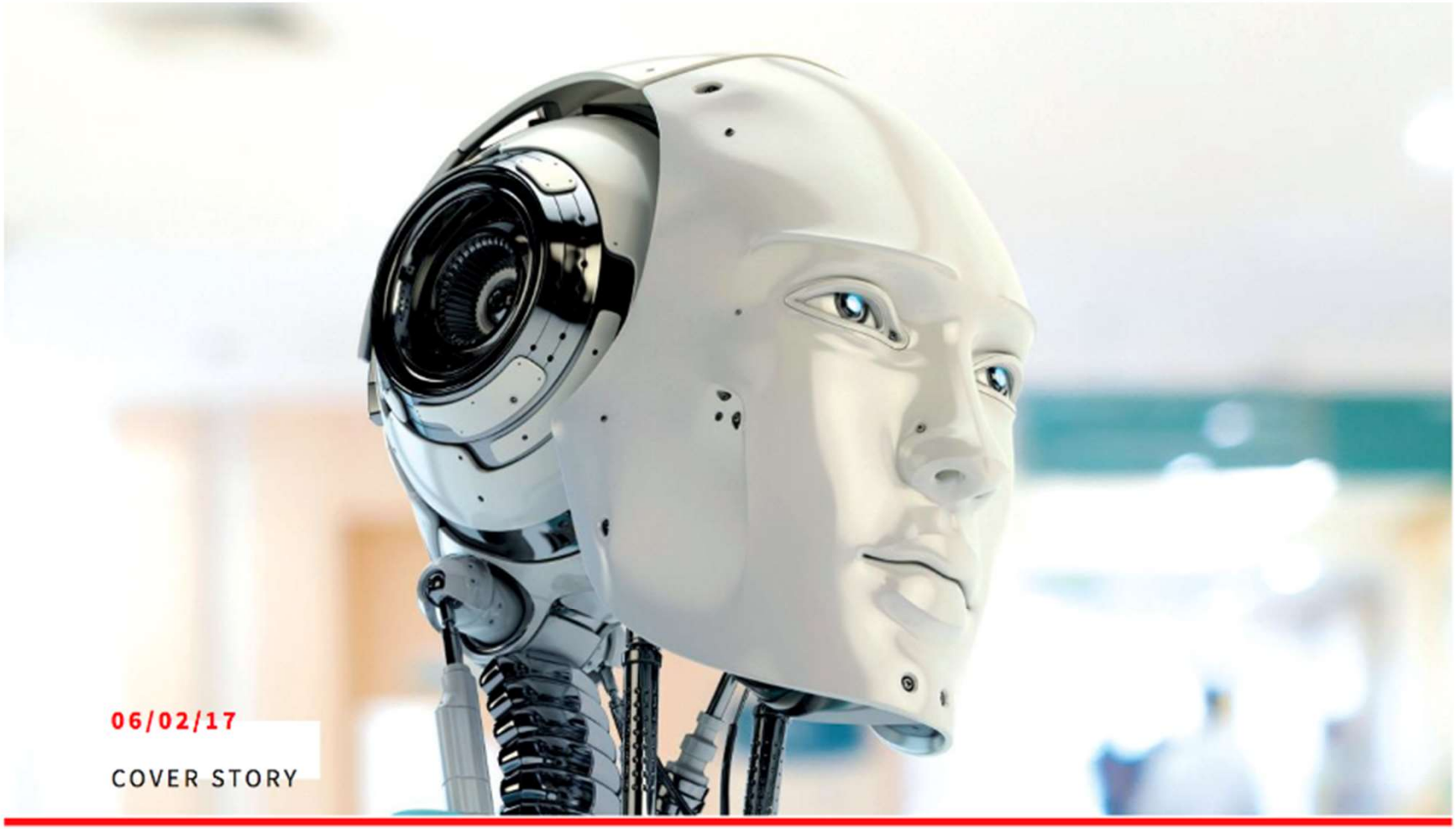
Personalized medicine



TECH & SCIENCE

HOW ARTIFICIAL INTELLIGENCE WILL CURE AMERICA'S SICK HEALTH CARE SYSTEM

BY KEVIN MANEY ON 5/24/17 AT 9:27 AM



06/02/17

COVER STORY

Exclusive: Facebook plots first steps into healthcare

BY CHRISTINA FARR AND **ALEXEI ORESKOVIC**

SAN FRANCISCO | Fri Oct 3, 2014 4:50am EDT

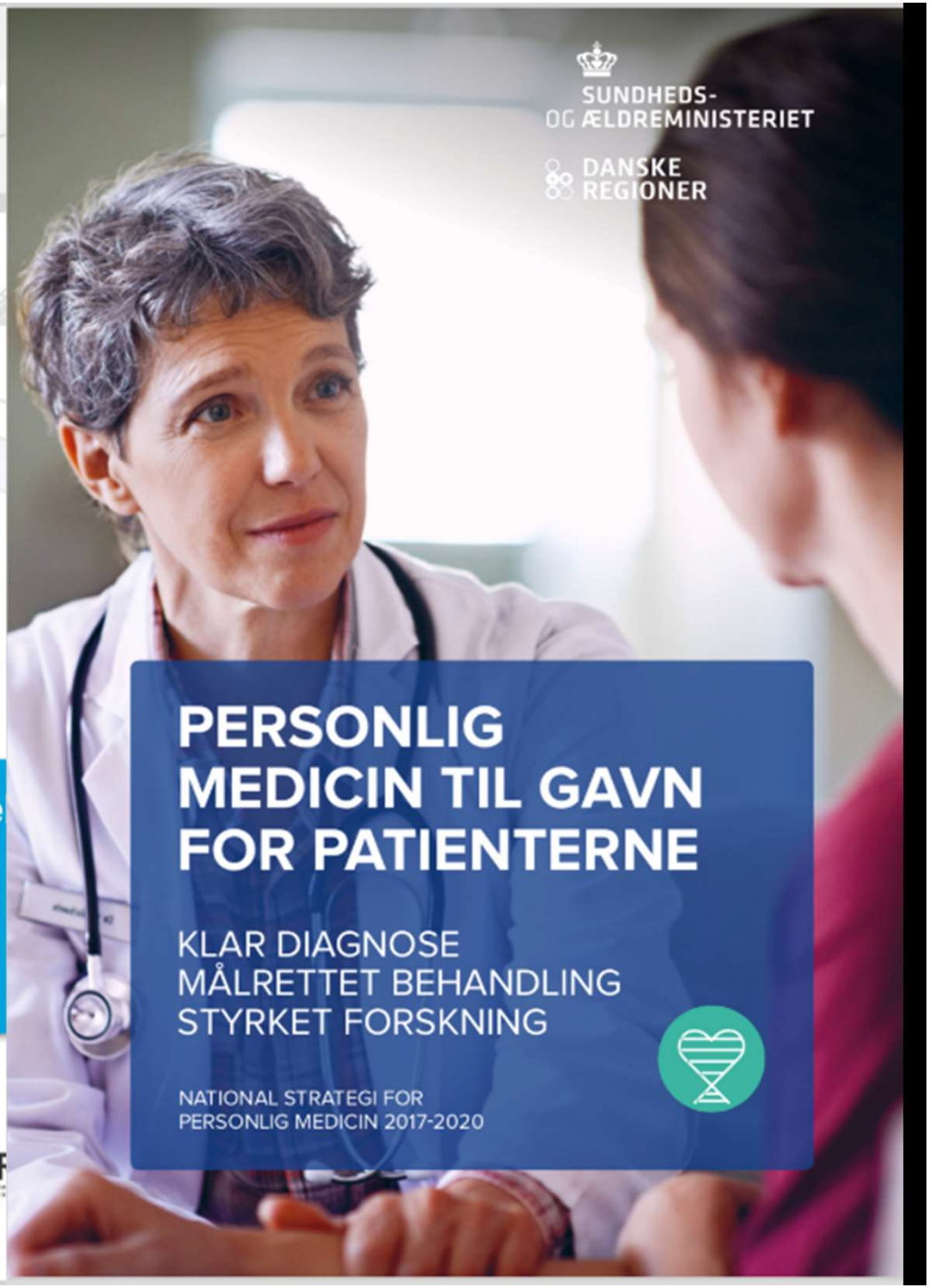
“You are the new doctor”

En personlig och digital vårdupplevelse - Framtidens primärvård

Rapport från det Vinnova-finansierade projektet *Nya förutsättningar för primärvården genom digitalisering.*

Kort version

SP apoteket VINNOVA INNOVATION SKÅNE



A vision with many names

A vision with many names


All of Us℠
THE FUTURE OF HEALTH BEGINS WITH YOU
The Precision Medicine Initiative®

Systems medicine: The topic

Bousquet *et al. Genome Medicine* 2011, 3:43
http://genomemedicine.com/content/3/7/43

Genome Medicine

CORRESPONDENCE Open Access

Systems medicine and integrated care to combat chronic noncommunicable diseases

Jean Bousquet[1*], Josep M Anto[2], Peter J Sterk[3], Ian M Adcock[4], Kian Fan Chung[5], Josep Roca[6], Alvar Agusti[6], Chris Brightling[7], Anne Cambon-Thomsen[8], Alfredo Cesario[9], Sonia Abdelhak[10], Stylianos E Antonarakis[11], Antoine Avignon[12], Andrea Ballabio[13], Eugenio Baraldi[14], Alexander Baranov[15], Thomas Bieber[16], Joël Bockaert[17], Samir Brahmachari[18], Christian Brambilla[19], Jacques Bringer[20], Michel Dauzat[21], Ingemar Ernberg[22], Leonardo Fabbri[23], Philippe Froguel[24], David Galas[25], Takashi Gojobori[26], Peter Hunter[27], Christian Jorgensen[28], Francine Kauffmann[29], Philippe Kourilsky[30], Marek L Kowalski[31], Doron Lancet[32], Claude Le Pen[33], Jacques Mallet[34], Bongani Mayosi[35], Jacques Mercier[36], Andres Metspalu[37], Joseph H Nadeau[25], Grégory Ninot[38], Denis Noble[39], Mehmet Öztürk[40], Susanna Palkonen[41], Christian Préfaut[16], Klaus Rabe[42], Eric Renard[20], Richard G Roberts[43], Boleslav Samolinski[44], Holger J Schünemann[45], Hans-Uwe Simon[46], Marcelo Bento Soares[47], Giulio Superti-Furga[48], Jesper Tegner[49], Sergio Verjovski-Almeida[50], Peter Wellstead[51], Olaf Wolkenhauer[52], Emiel Wouters[53], Rudi Balling[54], Anthony J Brookes[55], Dominique Charron[56], Christophe Pison[57,58], Zhu Chen[59], Leroy Hood[25] and Charles Auffray[56,57,58,60,61]

Abstract

We propose an innovative, integrated, cost-effective health system to combat major non-communicable diseases (NCDs), including cardiovascular, chronic respiratory, metabolic, rheumatologic and neurologic disorders and cancers, which together are the predominant health problem of the 21st century. This proposed holistic strategy involves comprehensive patient-centered

Non-communicable diseases, the major global health problem of the century

Chronic diseases are disorders of long duration and generally slow progression [1]. They include four major non-communicable diseases (NCDs) listed by the World Health Organization (WHO) [2] – cardiovascular diseases, cancer, chronic respiratory diseases and diabetes – as well as other NCDs, such as

The promises of P4 medicine

- Personalized medicine:
  - A form of medicine that can account for “those factors” that define health and disease in each particular person.
- Predictive and preventive medicine
  - A medicine that – based on knowledge about “those factors” can not only diagnose and treat disease in the present more accurately and precisely, but predict disease in the future and enable preventive interventions.
- Participatory medicine
  - A medicine in which persons or patients are enabled to *know themselves and to take control* of their health through technology and so drive the revolution.

The promise of P4 medicine and systems medicine

In sum, the main **promise** of P4 medicine is *a revolution* in the utility of individualized preventive medicine through a new holism.

Curative vs preventive precision medicine


IS-2446
Helsedirektoratet
Nasjonal strategi for persontilpasset medisin i helsetjenesten
2017-2021

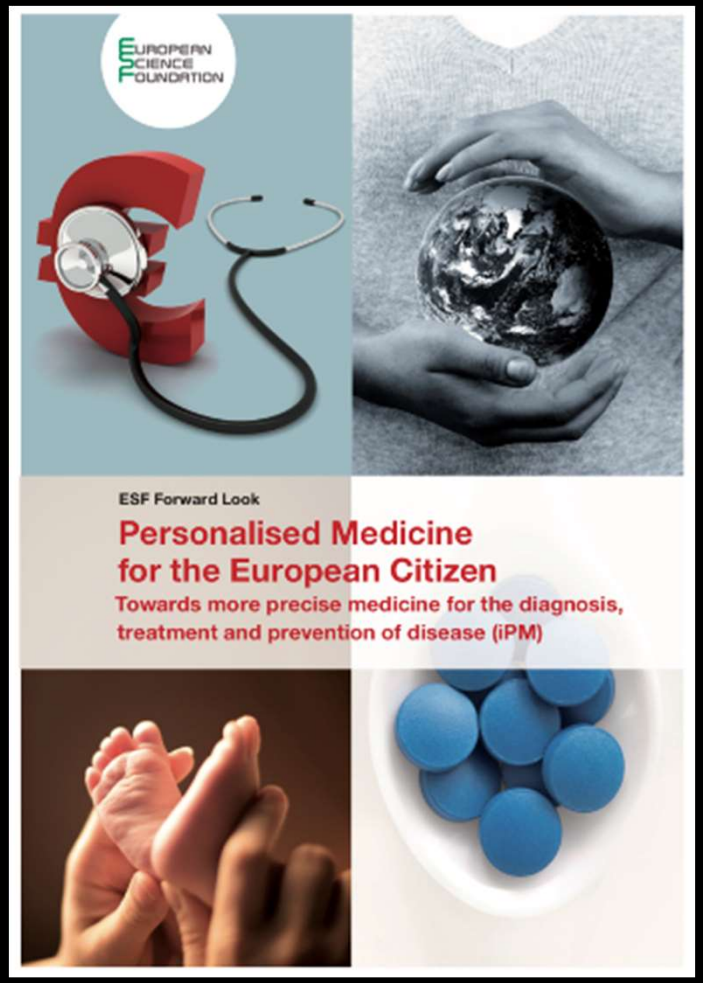
- «An important and exciting new field that will change healthcare. The aim is to give patients more precise and targeted diagnostics and treatment, og at the same time avoid treatment that has no effect».
  - What about diagnostics that harms, but leads nowhere? (overdiagnosis).
- «The main theme in the strategy is genetic large scale analyses, which is new in the clinic».
- «Primary health care should also be involved in this development».

- «An important and exciting new field that will change healthcare. The aim is to give patients more precise and targeted diagnostics and treatment, og at the same time avoid treatment that has no effect».
  - What about diagnostics that harms, but leads nowhere? (overdiagnosis).
- «The main theme in the strategy is genetic large scale analyses (genomic), which is new in the clinic».
- «Primary health care should also be involved in this development».

- «There is today uncertainty about the contents, scale and implementation of personalized medicine in general practice. Likely, general practitioners will in the future order more genetic tests for their patients and be contacted by well patients who have perfromed a genetic test on their own initiative. General practitioners will need to be able to inform patientsabiut simpler issues and know routines for when referral to genetic counselling is relevant. To achieve this goal, there is a need heightened competence where personalized Fmedicine and genetics is put in a larger context with among other things, ethics and patient-centered pedagogics».

Yes, genomic and other big data will give us personalized (precision) medicine (already here).

- Three areas
  - Rare diseases (monogenic, Mendelian)
  - Cancer medicine (tumor tailored)
  - Infection (bug tailored)



«In essence, personalised medicine represents a shift from reactive medicine to proactive, pre-emptive and preventive healthcare».


SUNDHEDS-
OG ÆLDREMINISTERIET
DANSKE
REGIONER
PERSONLIG
MEDICIN TIL GAVN
FOR PATIENTERNE
KLAR DIAGNOSE
MÅLRETTET BEHANDLING
STYRKET FORSKNING
NATIONAL STRATEGI FOR
PERSONLIG MEDICIN 2017-2020

- 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 medføre helt nye former for individualiseret behandling og livslang forebyggelse. Visionen er forebyggelse målrettet den enkelte borger og personlig behandling, når sygdommen rammer. (Danske Regioner 2015a: 5)

Medicalization

My definition: The way aspects of life become defined in medical terms and underlain medical control (Vogt et al., 2016)

Problems of controllability

A key assumption of P4SM is that it will provide people with a new level of motivation so that each person will change their lifestyle based on predictions (risk assessments).

Some downsides of medicalization

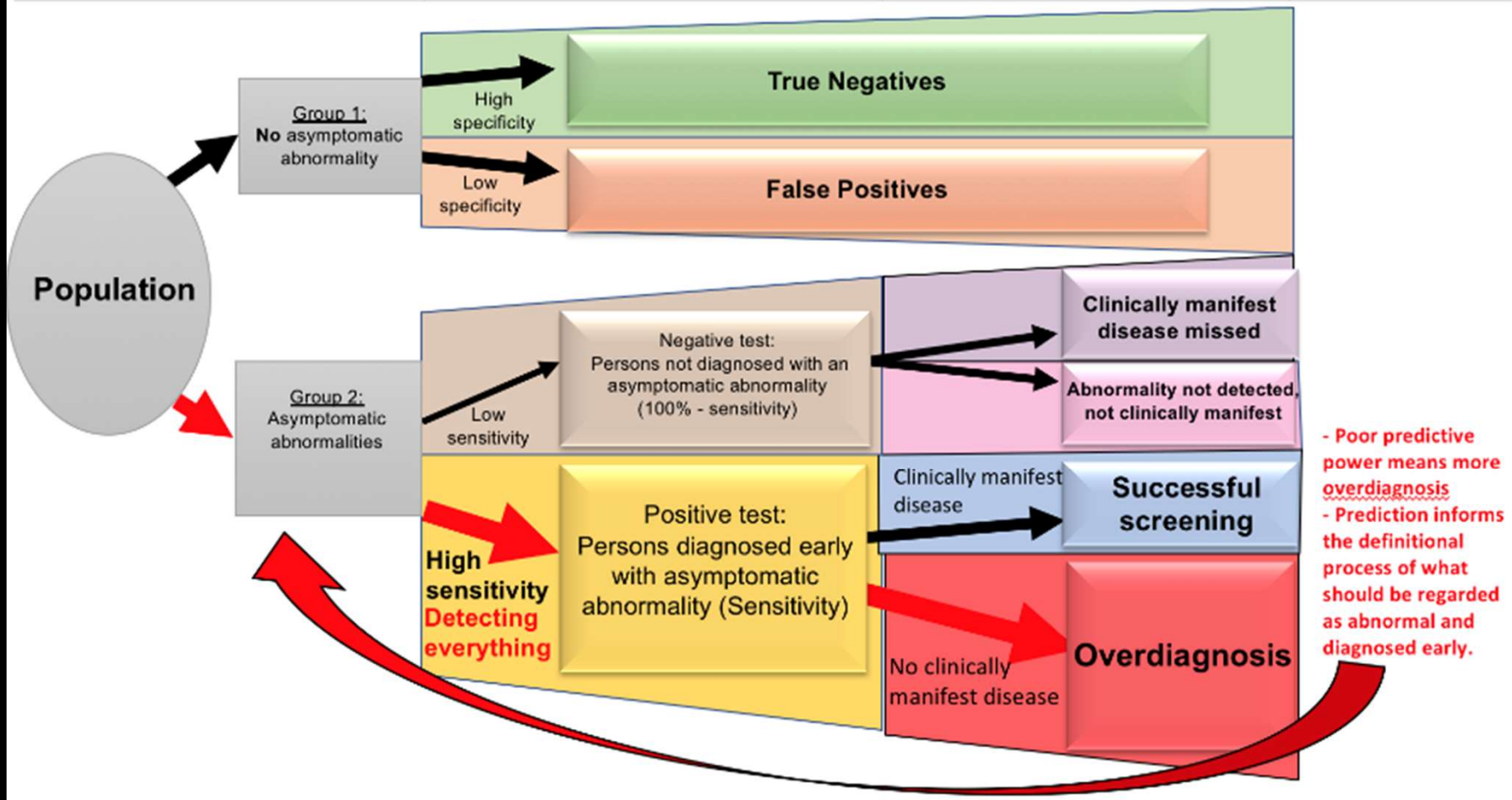
- Overdiagnosis
- False positive tests
- Findings of unknown significance
- Side-effects of diagnosis and treatment, including nocebo effects
- Worry
- Changes in identity
- Pathologization
- Depersonalization and dehumanization
- Increasing expectations of wellness or health
- Opportunity costs (distraction)
- Social and cultural iatrogenesis (Illich, 1976)
- Disempowerment, loss of freedom

Screening version 2.0

Source: Instutute for systems biology

What about overdiagnosis and big data?

Step A: Definitional process	Step B: Screening and detection	Step C: Time and observation	Step D: Prediction
Medicine defines what should be regarded as asymptomatic abnormalities to be screened for affecting the proportion of the population regarded as having abnormalities and the number of such abnormalities in each person.	Screening test determines how many are diagnosed early with the asymptomatic abnormality.	Time, observation, and further testing show which of the asymptomatic abnormalities are actually destined to become clinically manifest disease (symptoms or death).	Prediction of precisely which abnormalities will become clinically manifest disease



The screening of everyone

Screening for many abnormalities/diseases

The detection of «everything»

Step A: Definitional process	Step B: Screening and detection	Step C: Time and observation	Step D: Prediction
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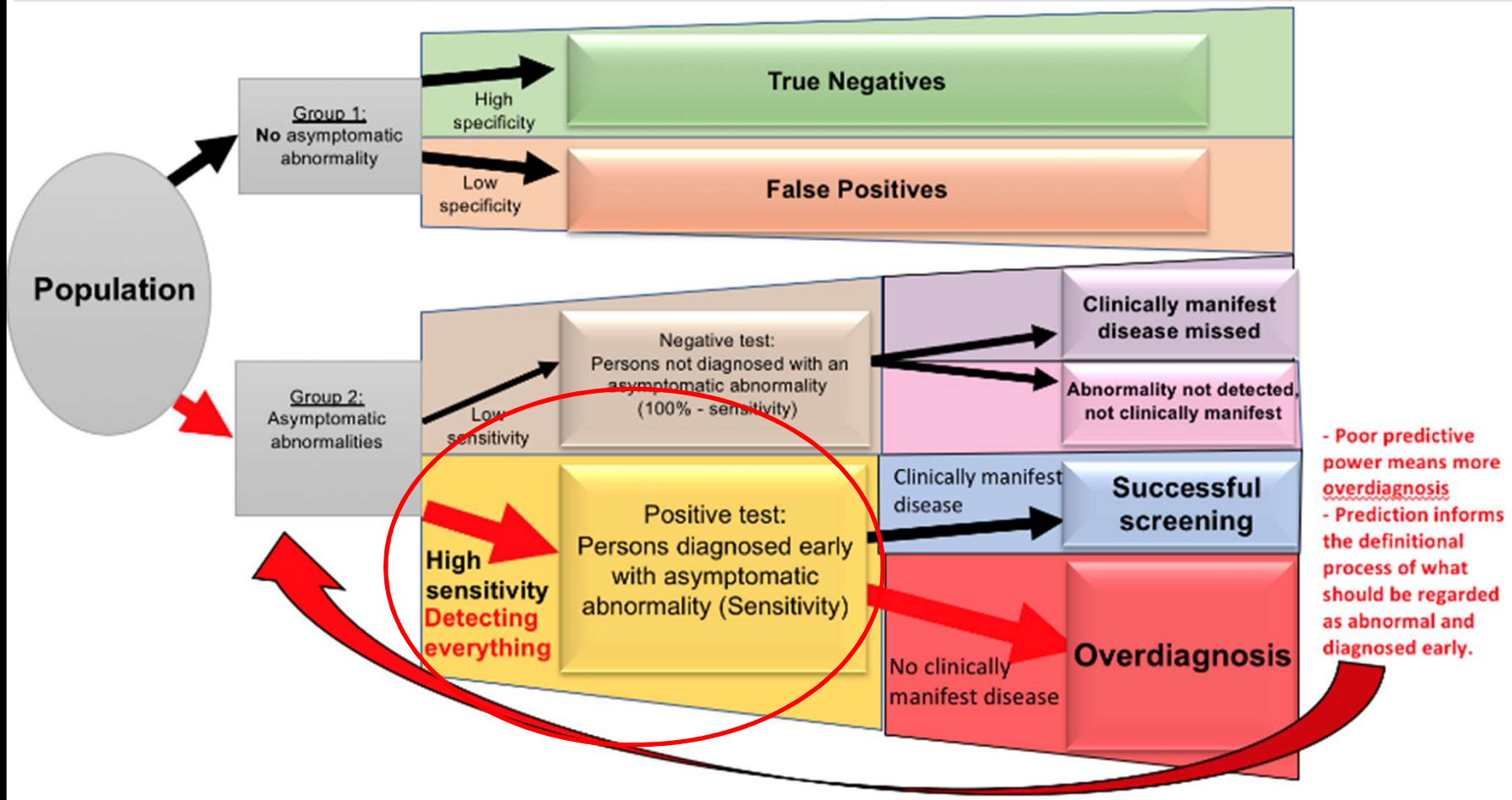

The premise to avoid increased overdiagnosis:

To predict just which abnormalities will become clinically manifest, and which will not,

in each person.

Step A: Definitional process	Step B: Screening and detection	Step C: Time and observation	Step D: Prediction
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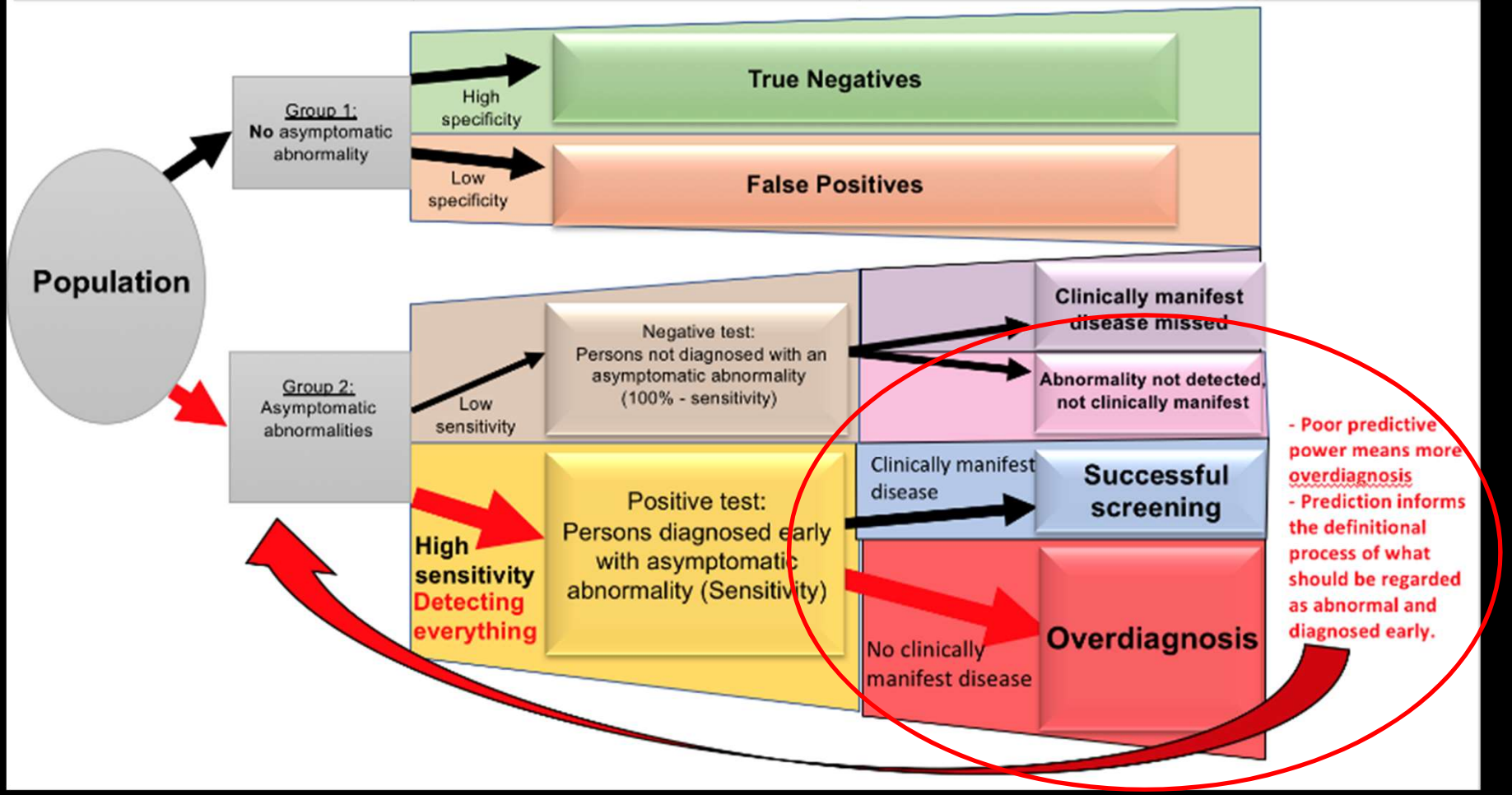

Can big data precision medicine do this?

Can precision medicine do good?

Where are we today?

Genetic testing: Some history

The case of the missing heritability

When scientists opened up the human genome, they expected to find the genetic components of common traits and diseases. But they were nowhere to be seen. **Brendan Maher** shines a light on six places where the missing loot could be stashed away.

nature genetics

LETTERS

https://doi.org/10.1038/s41588-018-0183-z

Genome-wide polygenic scores for common diseases identify individuals with risk equivalent to monogenic mutations

Amit V. Khera[1,2,3,4,5], Mark Chaffin[4,5], Krishna G. Aragam[1,2,3,4], Mary E. Haas[4], Carolina Roselli[4], Seung Hoan Choi[4], Pradeep Natarajan[2,3,4], Eric S. Lander[4], Steven A. Lubitz[2,3,4], Patrick T. Ellinor[2,3,4] and Sekar Kathiresan[1,2,3,4*]

A key public health need is to identify individuals at high risk for a given disease to enable enhanced screening or preventive therapies. Because most common diseases have a genetic component, one important approach is to stratify individuals based on inherited DNA variation[1]. Proposed clinical applications have largely focused on finding carriers of rare monogenic mutations at several-fold increased risk. Although most disease risk is polygenic in nature[2–5], it has not yet been possible to use polygenic predictors to identify individuals at risk comparable to monogenic mutations. Here, we develop and validate genome-wide polygenic scores for five common diseases. The approach identifies 8.0, 6.1, 3.5, 3.2, and 1.5% of the population at greater than threefold increased risk for coronary artery disease, atrial fibrillation, type 2 diabetes, inflammatory bowel disease, and breast cancer, respectively. For coronary artery disease, this prevalence is 20-fold higher than the carrier frequency of rare monogenic mutations conferring comparable risk[6]. We propose that it is time to contemplate the inclusion of polygenic risk prediction in clinical care, and discuss relevant issues.

Previous studies to create GPSs had only limited success, providing insufficient risk stratification for clinical utility (for example, identifying 20% of a population at 1.4-fold increased risk relative to the rest of the population)[12]. These initial efforts were hampered by three challenges: (1) the small size of initial genome-wide association studies (GWASs), which affected the precision of the estimated impact of individual variants on disease risk; (2) limited computational methods for creating GPSs; and (3) a lack of large datasets needed to validate and test GPS.

Using much larger studies and improved algorithms, we set out to revisit the question of whether a GPS can identify subgroups of the population with risk approaching or exceeding that of a monogenic mutation. We studied five common diseases with major public health impact: CAD, atrial fibrillation, type 2 diabetes, inflammatory bowel disease, and breast cancer.

For each of the diseases, we created several candidate GPSs based on summary statistics and imputation from recent large GWASs in participants of primarily European ancestry (Table 1). Specifically, we derived 24 predictors based on a pruning and thresholding method, and 7 additional predictors using the recently described

nature genetics

LETTERS

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OVERDIAGNOSIS?

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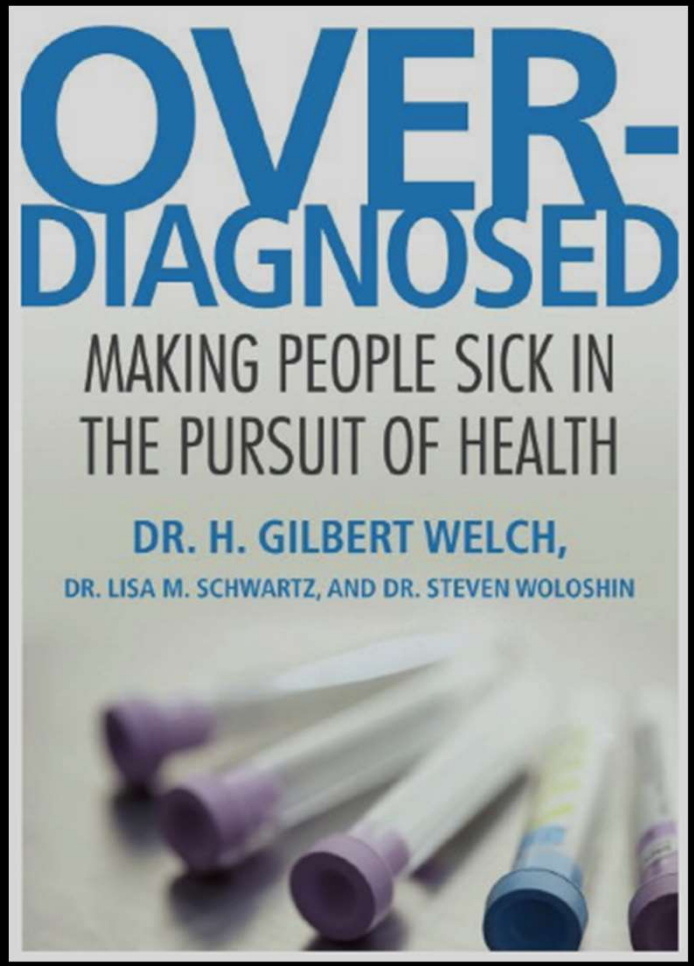
Can the new algorithm «undiagnose» as many people who would never have developed disease as it creates more overdiagnosis?

«Genetic testing is the most extreme manifestation of early diagnosis. (…) Because everybody is at risk of something, it´s a strategy that will literally make us all sick (…)»[1]



1) Welch, H; Lisa S.; Woloshin, S. 2011. Overdiagnosed (Chapter 9).

ARTICLES

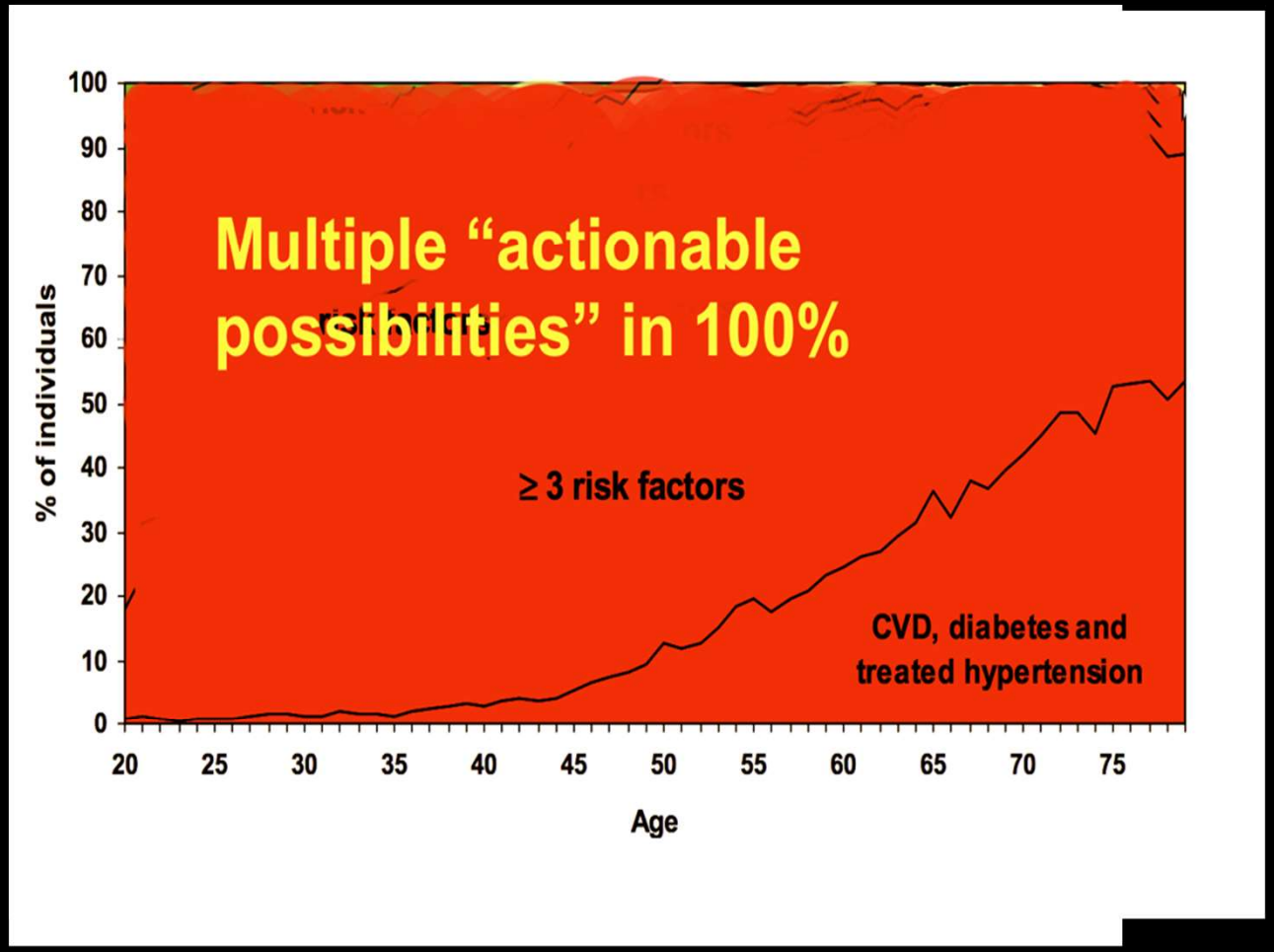
A wellness study of 108 individuals using personal, dense, dynamic data clouds

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.

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).



Referanser: Petursson et al. (2009), Price et al. (2017).

PNAS PNAS 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 of Medicine, San Diego, CA 92037; [e]Psychology and Neuroscience, University of Colorado, Boulder, CO 80309; [f]Department of Neurosciences, University of California, San Diego School of Medicine, San Diego, CA 92093; [g]Department of Radiology, University of California, San Diego School of Medicine, San Diego, CA 92093; [h]Metabolon, Morrisville, NC 27713; and [i]J. Craig Venter Research Institute, San Diego, CA 92037

Contributed by C. Thomas Caskey, August 9, 2017 (sent for review April 12, 2017; review

Reducing premature mortality associated with age-related chronic diseases, such as cancer and cardiovascular disease, is an urgent priority. We report early results using genomics in combination with advanced imaging and other clinical testing to proactively screen for age-related chronic disease risk among adults. We enrolled active, symptom-free adults in a study of screening for age-related chronic 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 imaging along with other testing among active, symptom-free adults identified a broad set of complementary age-related chronic disease risks associated with premature mortality and strengthened WGS variant interpretation. This and other similarly designed screening approaches anchored by WGS and advanced imaging may have the potential to extend healthy life among active adults through improved prevention and early detection of age-related chronic diseases (and their risk factors) associated with premature mortality.

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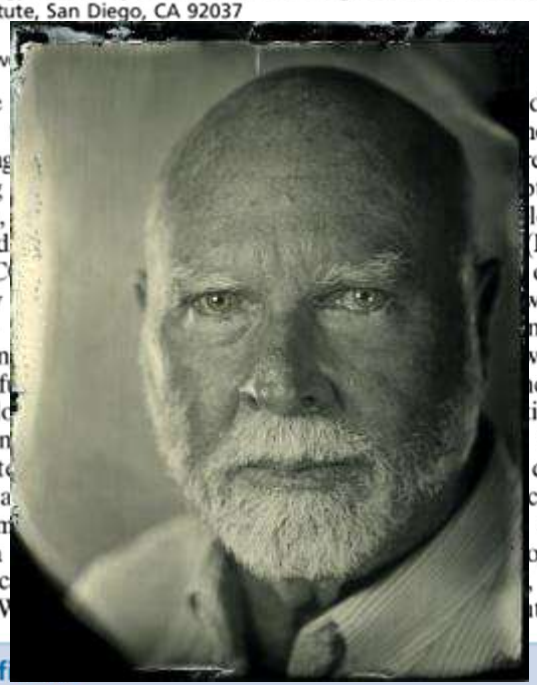

MEDICAL SCIENCES

Signif

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

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

How far can we get in prediction just what abnormalites will become clinically manifest?

Problems of predictability in complex biological systems

Bias-variance tradeoff

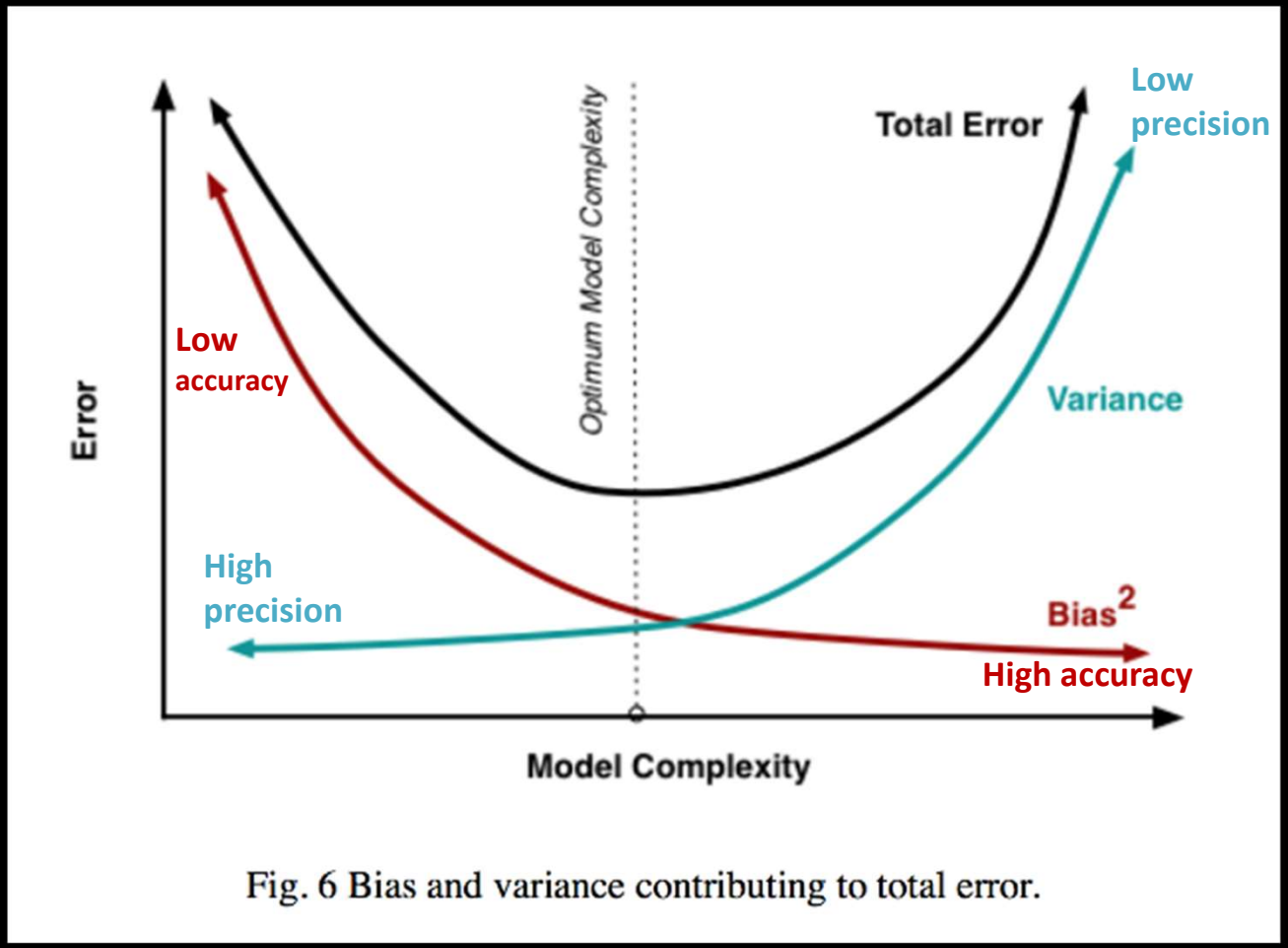

Fig. 6 Bias and variance contributing to total error.

Reference: Fortmann (2012), http://scott.fortmann-roe.com/docs/BiasVariance.html

Precision medicine → imprecision medicine


«Bog data»

”In fact, chaos (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[1]

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

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PLOS ONE

Whole-Genome Sequencing of the World's Oldest People

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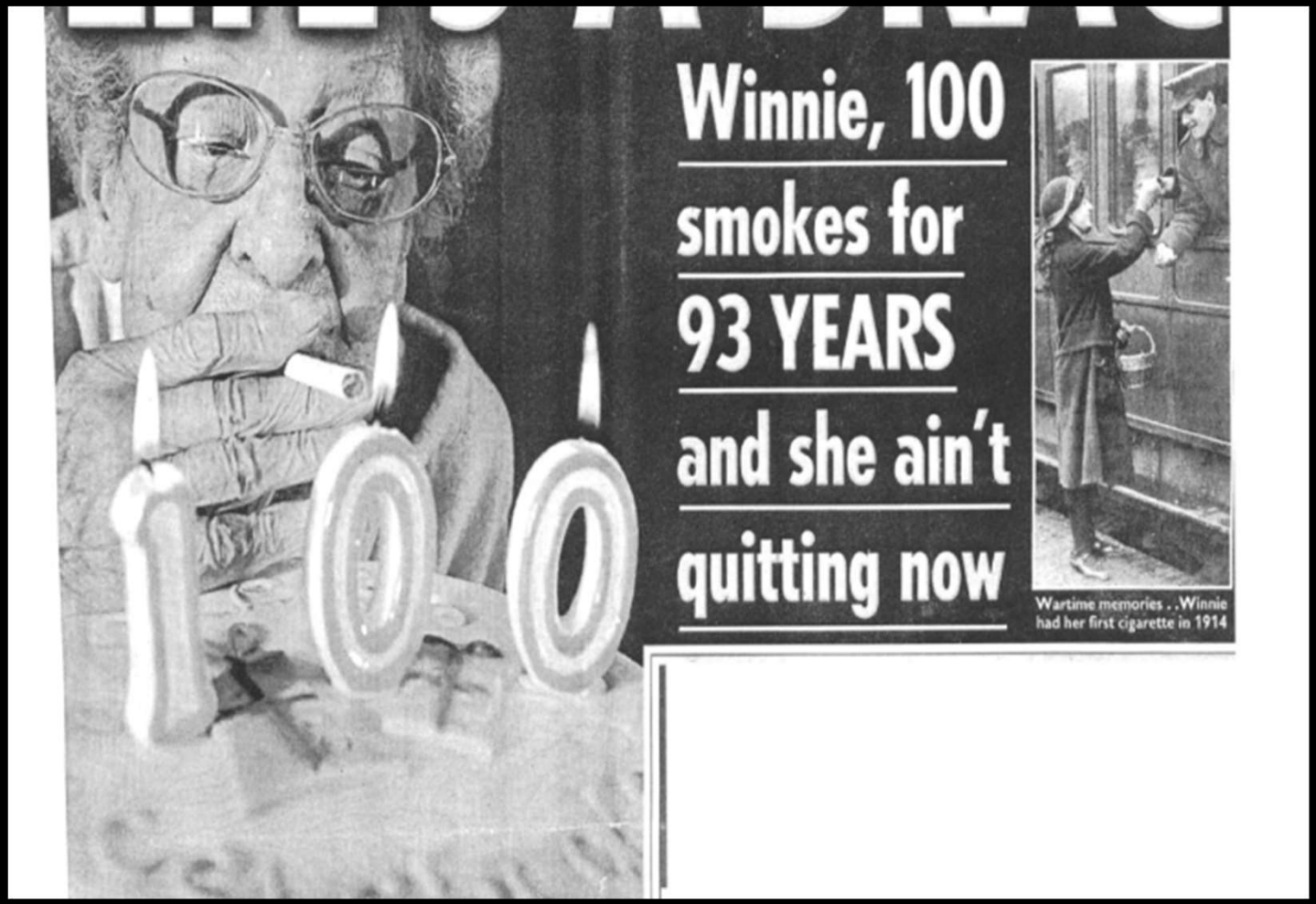
Abstract

Supercentenarians (110 years or older) are the world's oldes the United States. We performed whole-genome sequen 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.

Randomness: Good luck, bad luck



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

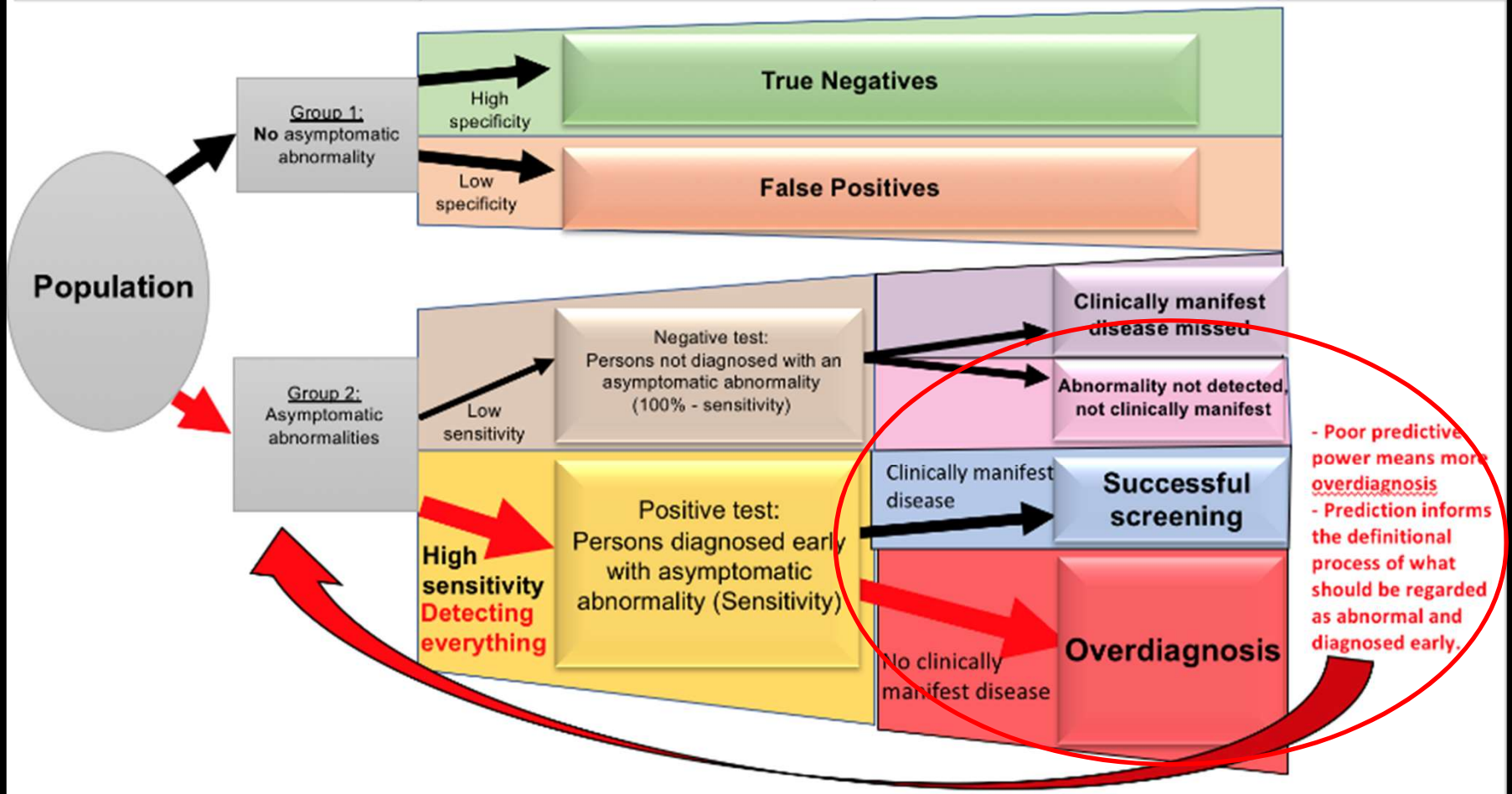
Conclusion

There are limits to predicting just what abnormalities will lead to symptomatic disease.

When “everything” abnormal is detected, big data risks increasing overdiagnosis more than it can reduce the problem.

A question of patience

Step A: Definitional process	Step B: Screening and detection	Step C: Time and observation	Step D: Prediction
Medicine defines what should be regarded as asymptomatic abnormalities to be screened for affecting the proportion of the population regarded as having abnormalities and the number of such abnormalities in each person.	Screening test determines how many are diagnosed early with the asymptomatic abnormality.	Time, observation, and further testing show which of the asymptomatic abnormalities are actually destined to become clinically manifest disease (symptoms or death).	Prediction of precisely which abnormalities will become clinically manifest disease



A question of tolerance

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