Quantitative Human Phenotyping: Opportunities for Convergent Science in the Novel Measurement of Health and Disease

Dennis Ausiello, M.D.
Founder and Director,
Center for Assessment Technology and Continuous Health (CATCH)

Physician-in-Chief *Emeritus*, MGH

Jackson Distinguished Professor of Clinical Medicine,
Harvard Medical School

THE NATIONAL ACADEMIES

DIVISION ON EARTH AND LIFE STUDIES
Board on Life Sciences

A New Biology for the 21st Century

Committee on a New Biology for the 21st Century

Co-Chairs:

Thomas Connelly, DuPont Company

Phillip A. Sharp, MIT

THE NATIONAL ACADEMIES

Advisers to the Nation on Science, Engineering, and Medicine

National Academy of Sciences
National Academy of Engineering
Institute of Medicine
National Research Council

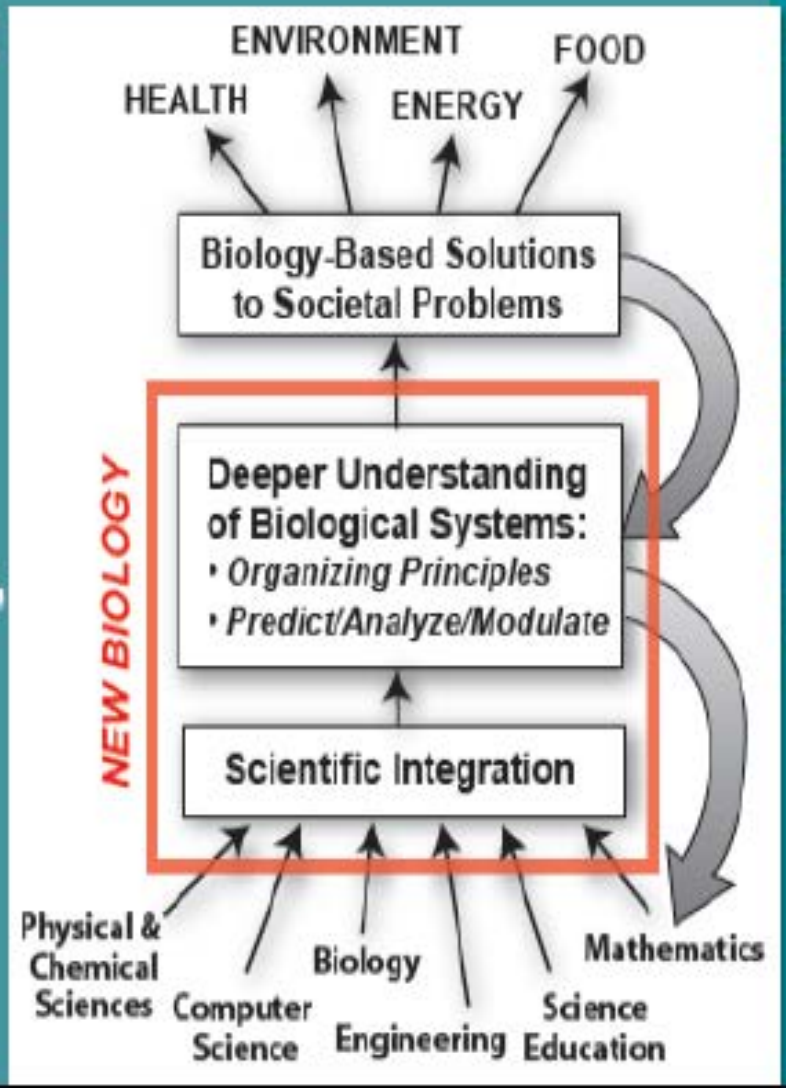
THE NATIONAL ACADEMIES

An opportunity for a New Biology with unprecedented impact

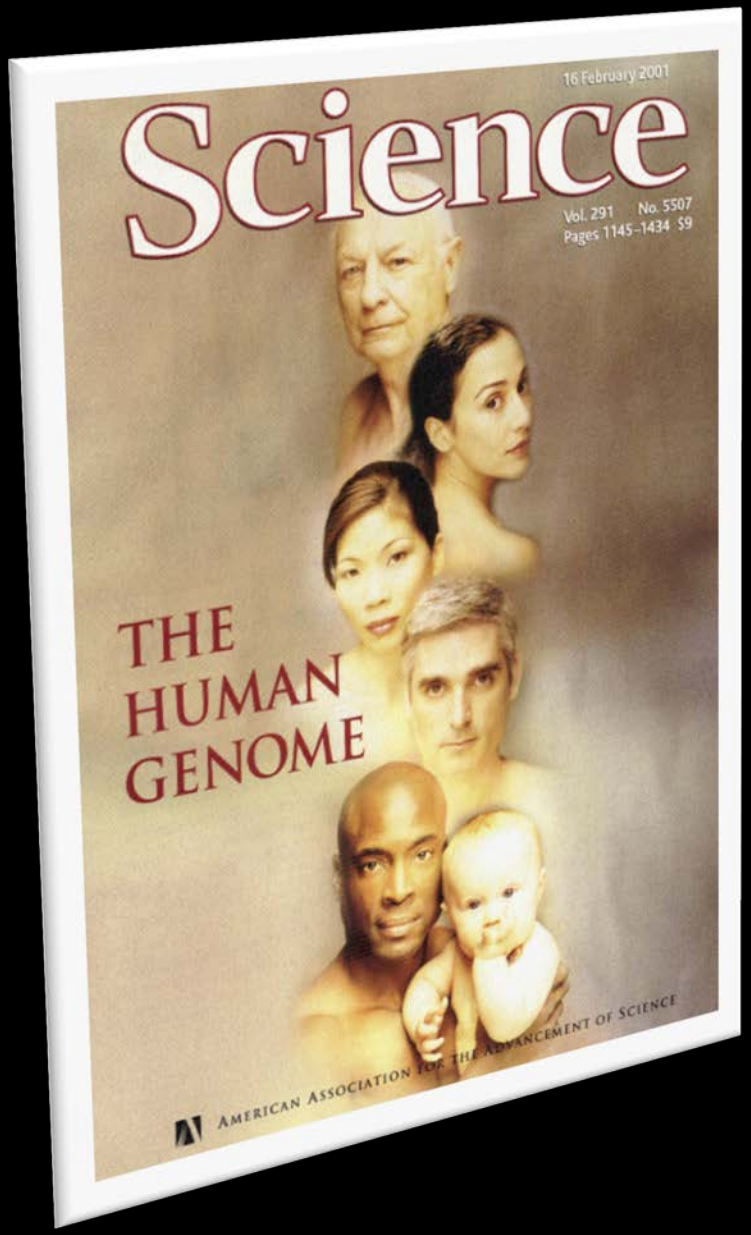
Integration of subdisciplines within biology

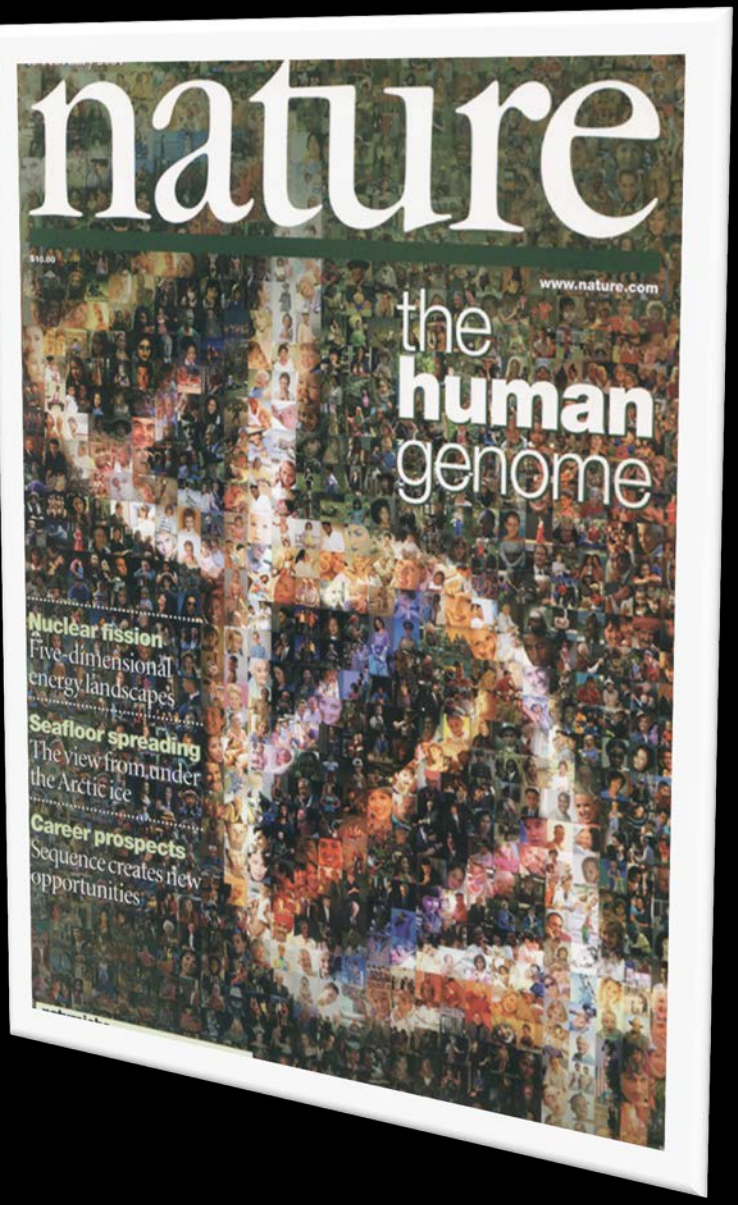
Cross-discipline integration: life science research performed by physical & computational scientists, engineers

Technological advances enable biologists to collect data unprecedented in quantity and quality



Promise and excitement of the human genome project





A success story for genetics: targeted therapies in oncology

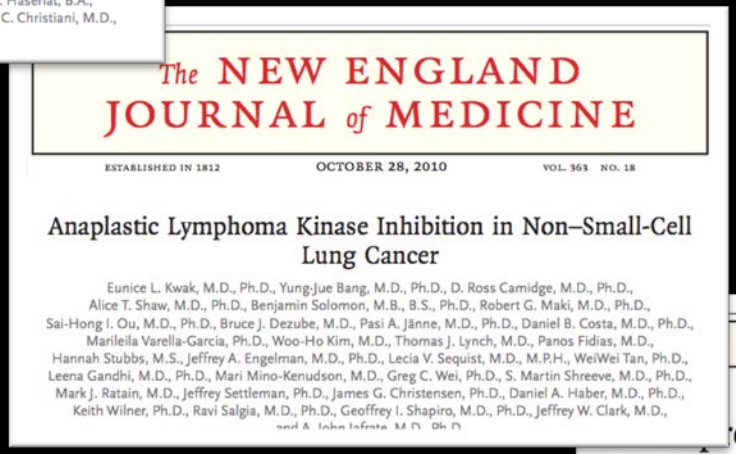
The NEW ENGLAND JOURNAL of MEDICINE

ESTABLISHED IN 1812 MAY 20, 2004 VOL. 350 NO. 21

Activating Mutations in the Epidermal Growth Factor Receptor Underlying Responsiveness of Non–Small-Cell Lung Cancer to Gefitinib

Thomas J. Lynch, M.D., Daphne W. Bell, Ph.D., Raffaella Sordella, Ph.D., Sarada Gurubhagavatula, M.D., Ross A. Okimoto, B.S., Brian W. Brannigan, B.A., Patricia L. Harris, M.S., Sara M. Haserlat, B.A., Jeffrey G. Supko, Ph.D., Frank G. Haluska, M.D., Ph.D., David N. Louis, M.D., David C. Christiani, M.D., Jeff Settleman, Ph.D., and Daniel A. Haber, M.D., Ph.D.

EGFR
(NSCLC)



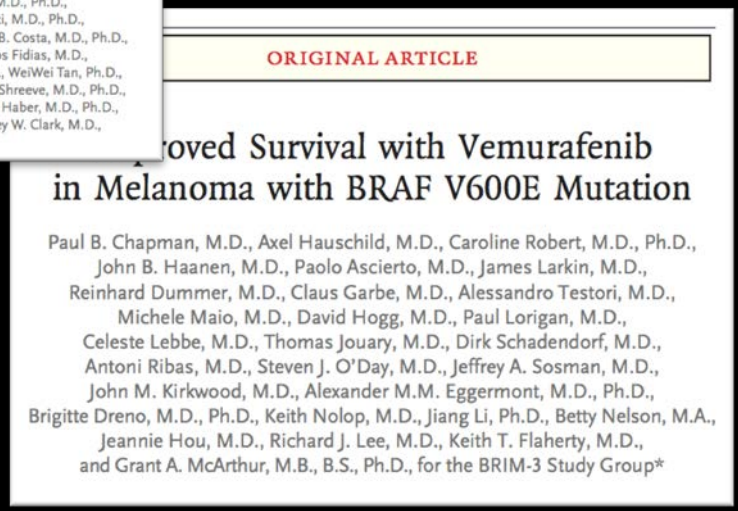
The NEW ENGLAND JOURNAL of MEDICINE

ESTABLISHED IN 1812 OCTOBER 28, 2010 VOL. 363 NO. 18

Anaplastic Lymphoma Kinase Inhibition in Non–Small-Cell Lung Cancer

Eunice L. Kwak, M.D., Ph.D., Yung-Jue Bang, M.D., Ph.D., D. Ross Camidge, M.D., Ph.D., Alice T. Shaw, M.D., Ph.D., Benjamin Solomon, M.B., B.S., Ph.D., Robert G. Maki, M.D., Ph.D., Sai-Hong I. Ou, M.D., Ph.D., Bruce J. Dezube, M.D., Pasi A. Jänne, M.D., Ph.D., Daniel B. Costa, M.D., Ph.D., Marileila Varella-Garcia, Ph.D., Woo-Ho Kim, M.D., Thomas J. Lynch, M.D., Panos Fidias, M.D., Hannah Stubbs, M.S., Jeffrey A. Engelman, M.D., Ph.D., Lecia V. Sequist, M.D., M.P.H., WeiWei Tan, Ph.D., Leena Gandhi, M.D., Ph.D., Mari Mino-Kenudson, M.D., Greg C. Wei, Ph.D., S. Martin Shreeve, M.D., Ph.D., Mark J. Ratain, M.D., Jeffrey Settleman, Ph.D., James G. Christensen, Ph.D., Daniel A. Haber, M.D., Ph.D., Keith Wilner, Ph.D., Ravi Salgia, M.D., Ph.D., Geoffrey I. Shapiro, M.D., Ph.D., Jeffrey W. Clark, M.D.,

ALK
(NSCLC)



ORIGINAL ARTICLE

roved Survival with Vemurafenib in Melanoma with BRAF V600E Mutation

Paul B. Chapman, M.D., Axel Hauschild, M.D., Caroline Robert, M.D., Ph.D., John B. Haanen, M.D., Paolo Ascierto, M.D., James Larkin, M.D., Reinhard Dummer, M.D., Claus Garbe, M.D., Alessandro Testori, M.D., Michele Maio, M.D., David Hogg, M.D., Paul Lorigan, M.D., Celeste Lebbe, M.D., Thomas Jouary, M.D., Dirk Schadendorf, M.D., Antoni Ribas, M.D., Steven J. O'Day, M.D., Jeffrey A. Sosman, M.D., John M. Kirkwood, M.D., Alexander M.M. Eggermont, M.D., Ph.D., Brigitte Dreno, M.D., Ph.D., Keith Nolop, M.D., Jiang Li, Ph.D., Betty Nelson, M.A., Jeannie Hou, M.D., Richard J. Lee, M.D., Keith T. Flaherty, M.D., and Grant A. McArthur, M.B., B.S., Ph.D., for the BRIM-3 Study Group*

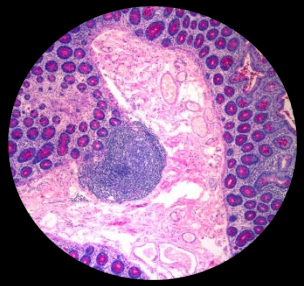
Braf
(Melanoma)

A success story for genetics: targeted therapies in oncology

Somatic mutations

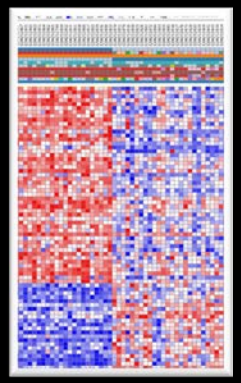
Routine sampling of patient cells

Unification of patient care and clinical discovery/research



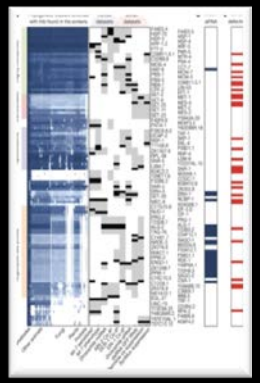
Histology

Genomics

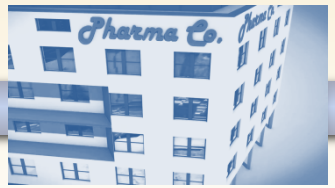


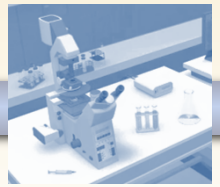
Molecular imaging

Chemical/ RNAi screens



Stratification 'rescues' a drug





2004

2004 Synthesis of crizotinib

2006

2006 Phase 1 trial (without genotyping activity)

2007

8/2007 EML4-ALK identified in NSCLC

12/2007 ALK+ NSCLC Phase 1 trial begins

2009

5/2009 First report of Crizotinib activity in ALK+ NSCLC pts (ASCO 2009)

2010

10/2010 NEJM publication of Phase 1 results

2011

08/2011 FDA APPROVAL

From description of genetic mutation (EML4-ALK) in non-small cell lung cancer to FDA approval:

4 years !

However, our ability to generalize this paradigm for chronic diseases remains limited !

The promise of the ‘genetic revolution’ for stratification of cardiovascular disease?

Accuracy predicting 10 year risk of CVD

	Using Risk Factors*
10 yr CVD	*0.787*

Risk Factors

Sex

Cholesterol

Smoking

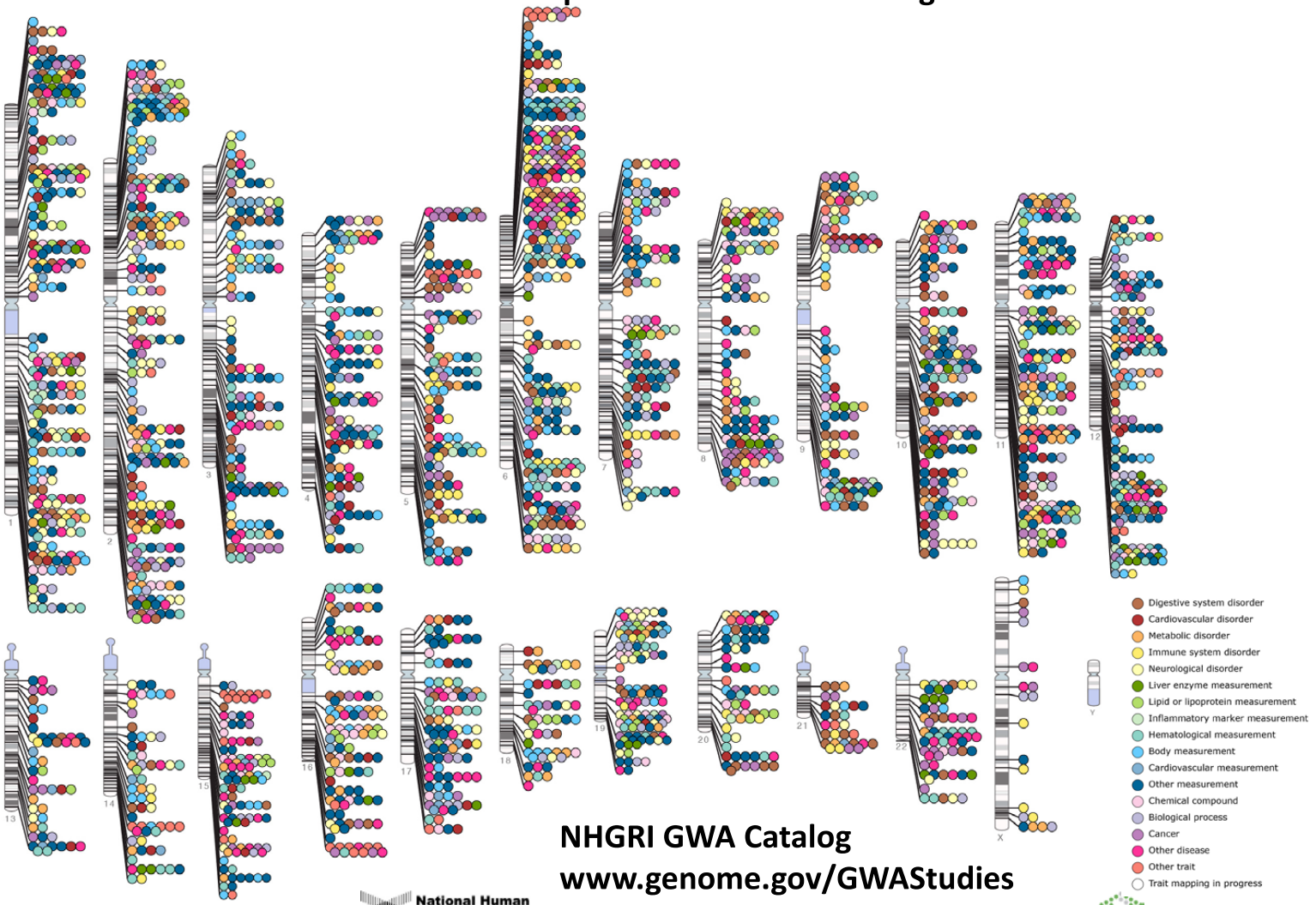
Age &
family history

Blood
pressure

Food

GWAS and the ‘genetic revolution’

Published Genome-Wide Associations through 07/2012
Published GWA at p≤5X10^{-8} for 18 trait categories



NHGRI GWA Catalog
www.genome.gov/GWAStudies
www.ebi.ac.uk/fgpt/gwas/

National Human Genome Research Institute

EMBL-EBI

The promise of the ‘genetic revolution’ for stratification of cardiovascular disease?

Accuracy predicting 10 year risk of CVD

	Using Risk Factors*	+ Genetic Risk Score
10 yr CVD	*0.787*	*0.788*

Risk Factors

Sex

Cholesterol

Smoking

Age &
family history

Blood
pressure

Food

Converging revolutions:

Genetic

Digital

Integrative Science

Measurements used in medicine have largely not changed

- Heart rate, blood pressure
- Height, weight
- Electrocardiogram (ECG)
- Blood glucose, hemoglobin A_1C
- Blood lipids

Center for Assessment Technology and Continuous Health

A renewed focus on phenotypes

The human phenotype must be measured

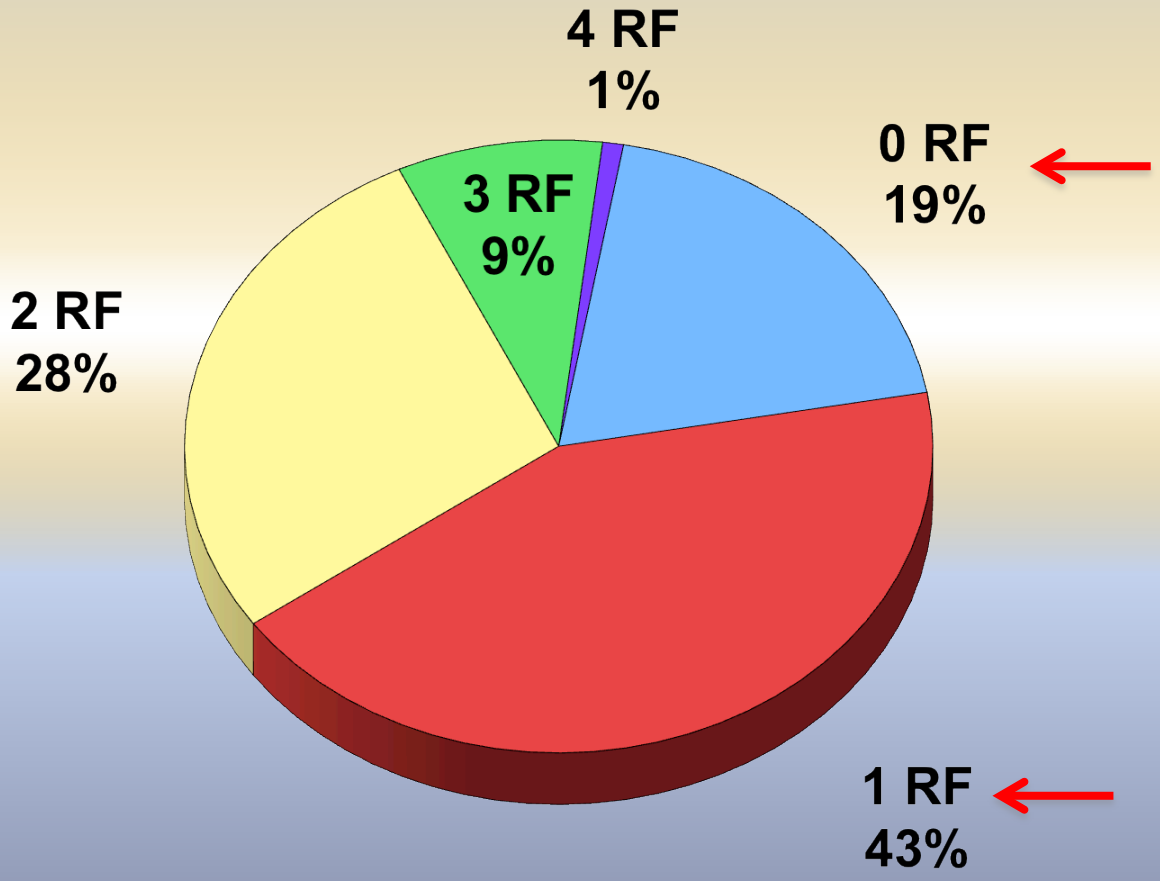
… with the same precision that we expect of genetic data

… in real-time to provide a perpetual read out

… in the context of multiple perturbations (such as drugs and environment)

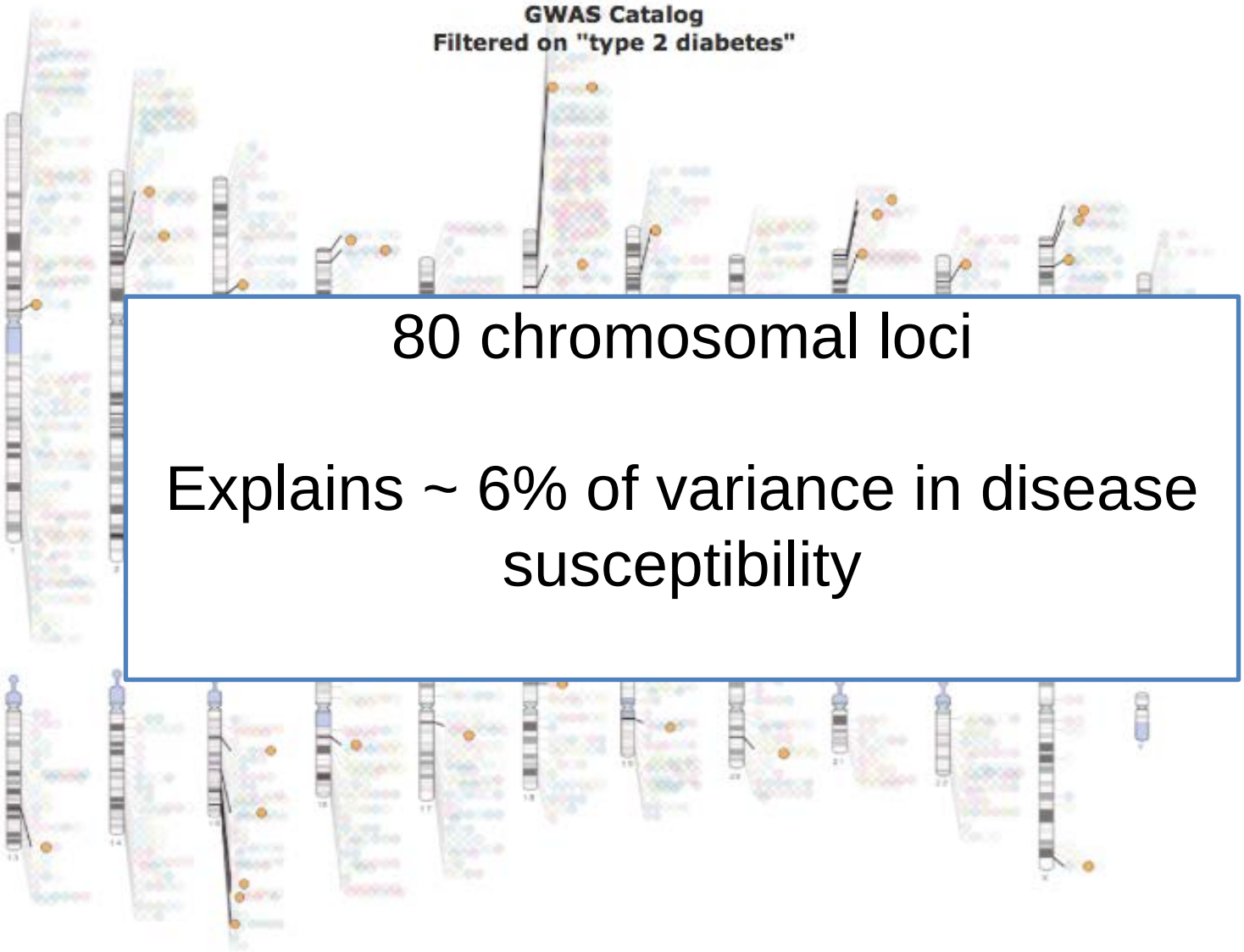
… and must ultimately create actionable new knowledge for healthcare performance

Not all individuals with coronary heart disease have traditional risk factors



Khott et al, JAMA 2003

Type 2 diabetes: increasing physiologic and genetic understanding



80 chromosomal loci

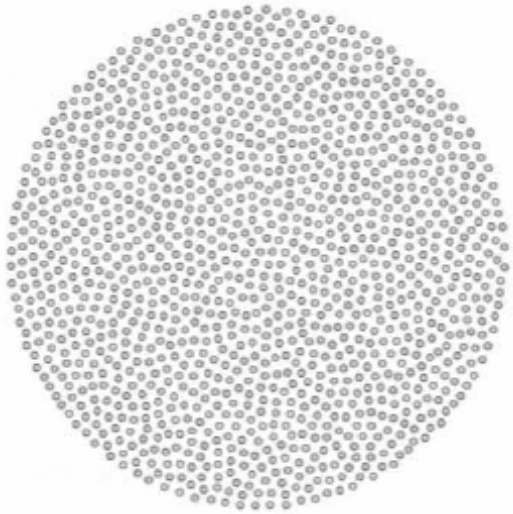
Explains ~ 6% of variance in disease susceptibility

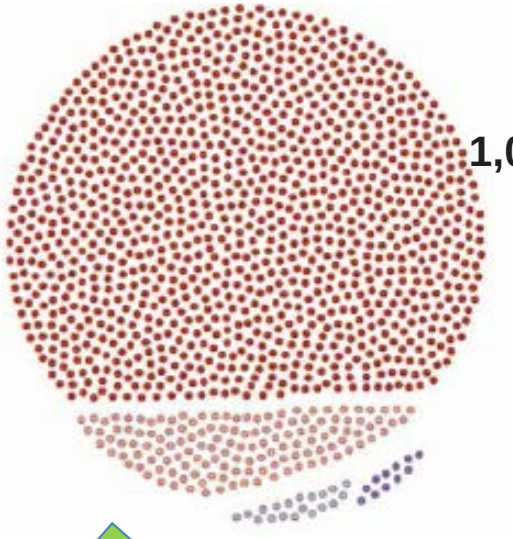
But what do we follow clinically?

BLACK BOX

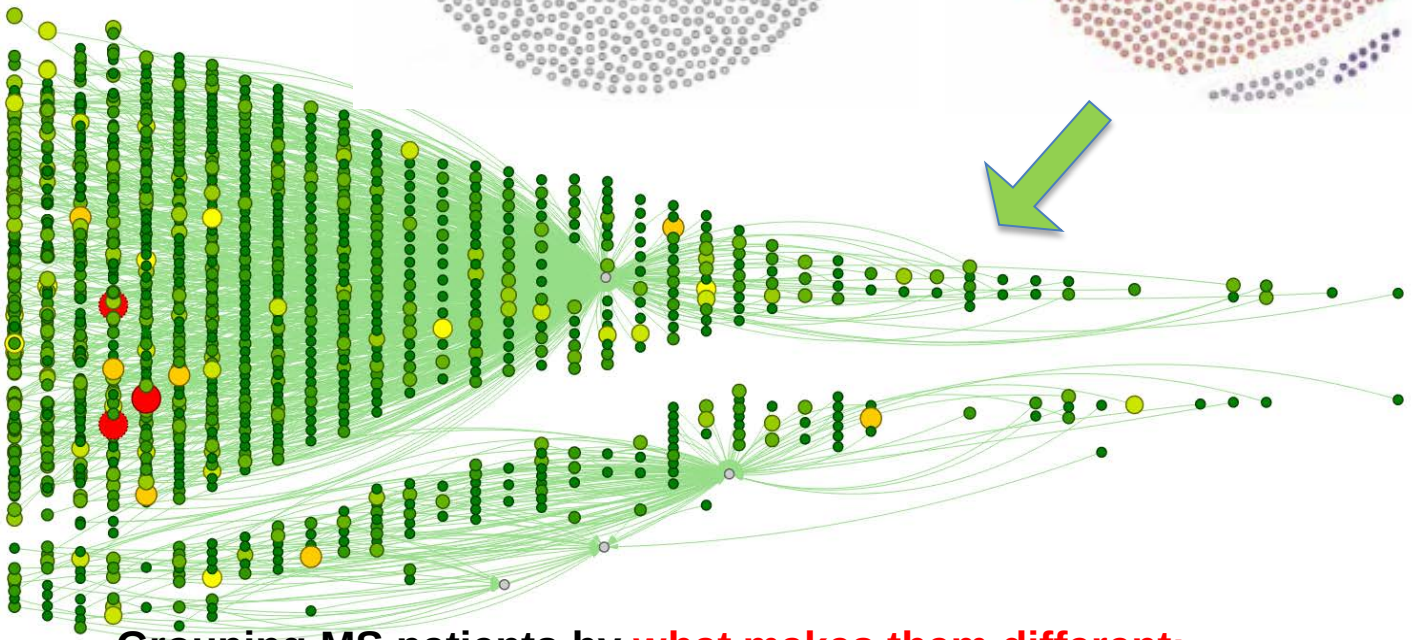
Unlocking what makes patients more different than the same - Data Analytics and Phenotyping

1,000 MS Patients: grouped by what they have in common





1,000 MS Patients: grouped by disease stage



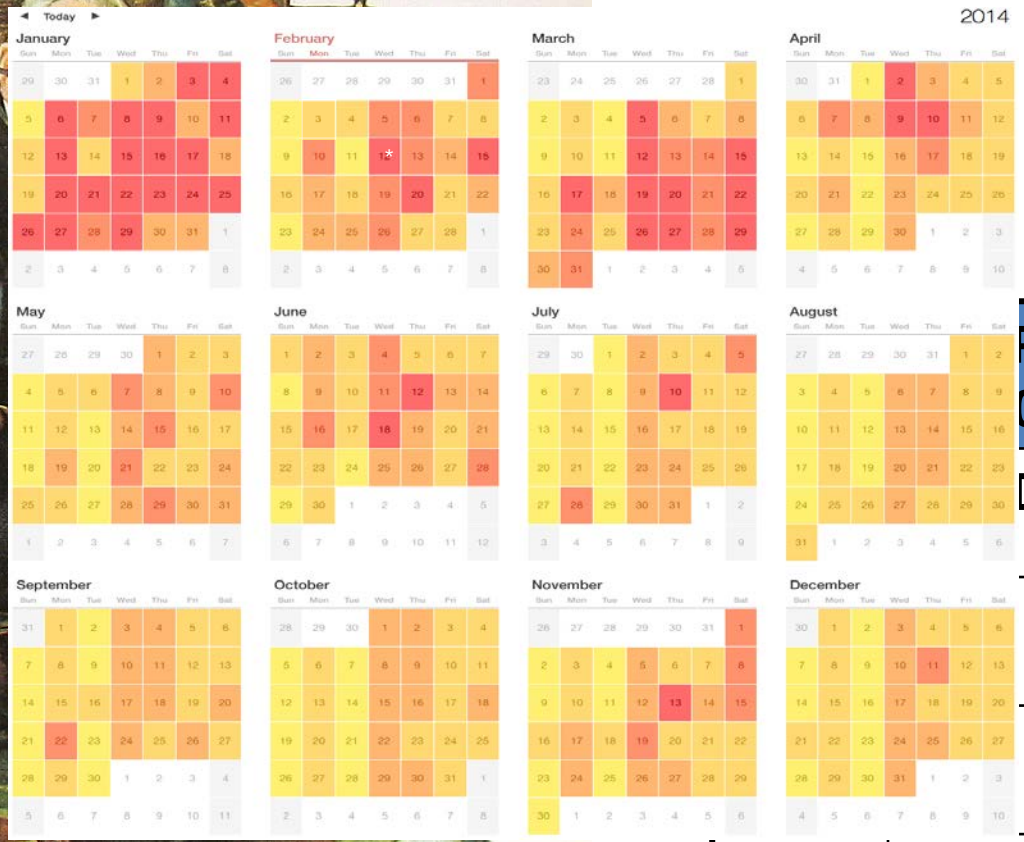
Grouping MS patients by what makes them different:
stratified by frequency of relapses, duration of disease, and severity of flares

exaptive

Episodic and Symptomatic

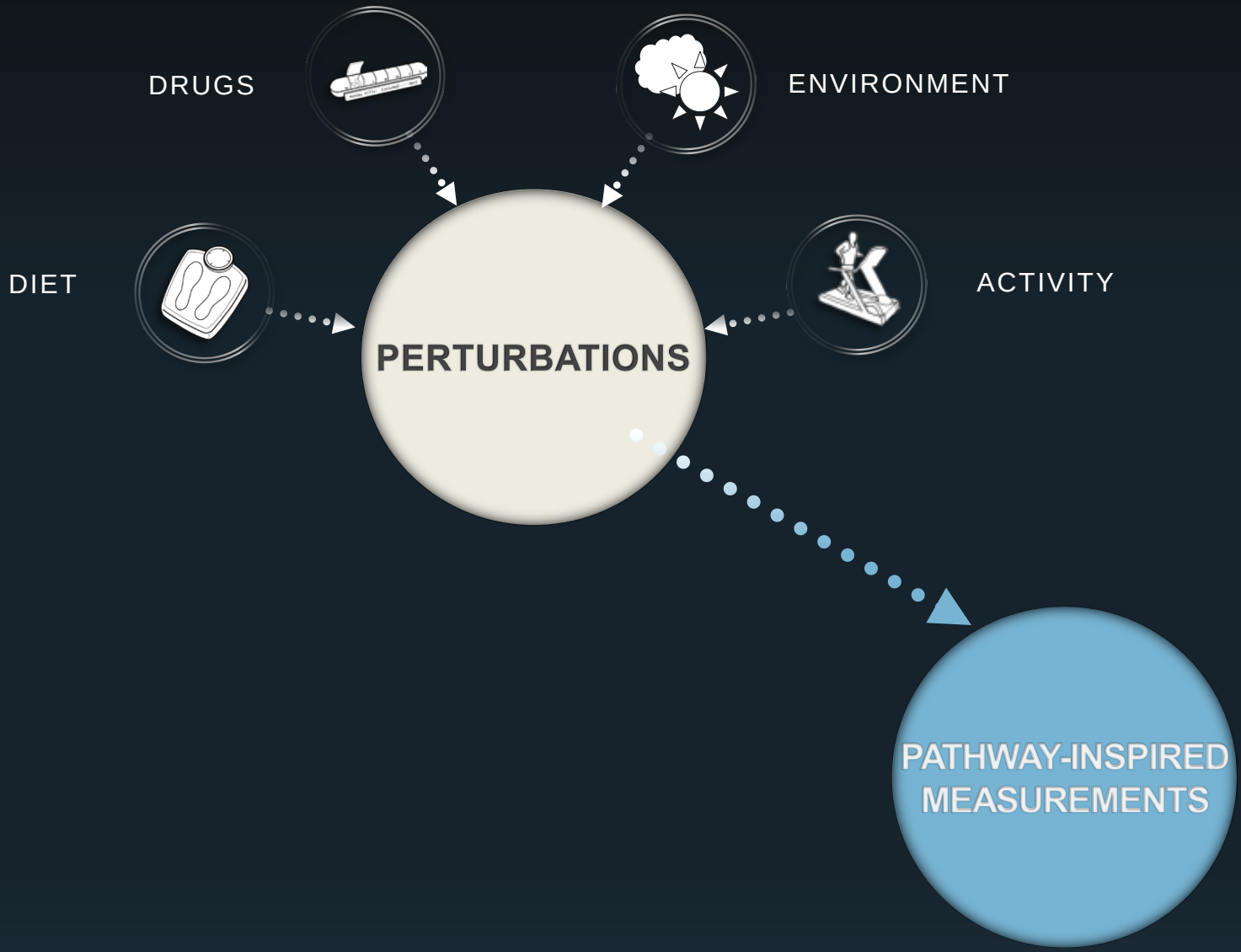
Saturday, February 15, 2014	
8:00	**Ms. Doe**
8:15	
8:45	
9:00	

Episodic and Symptomatic

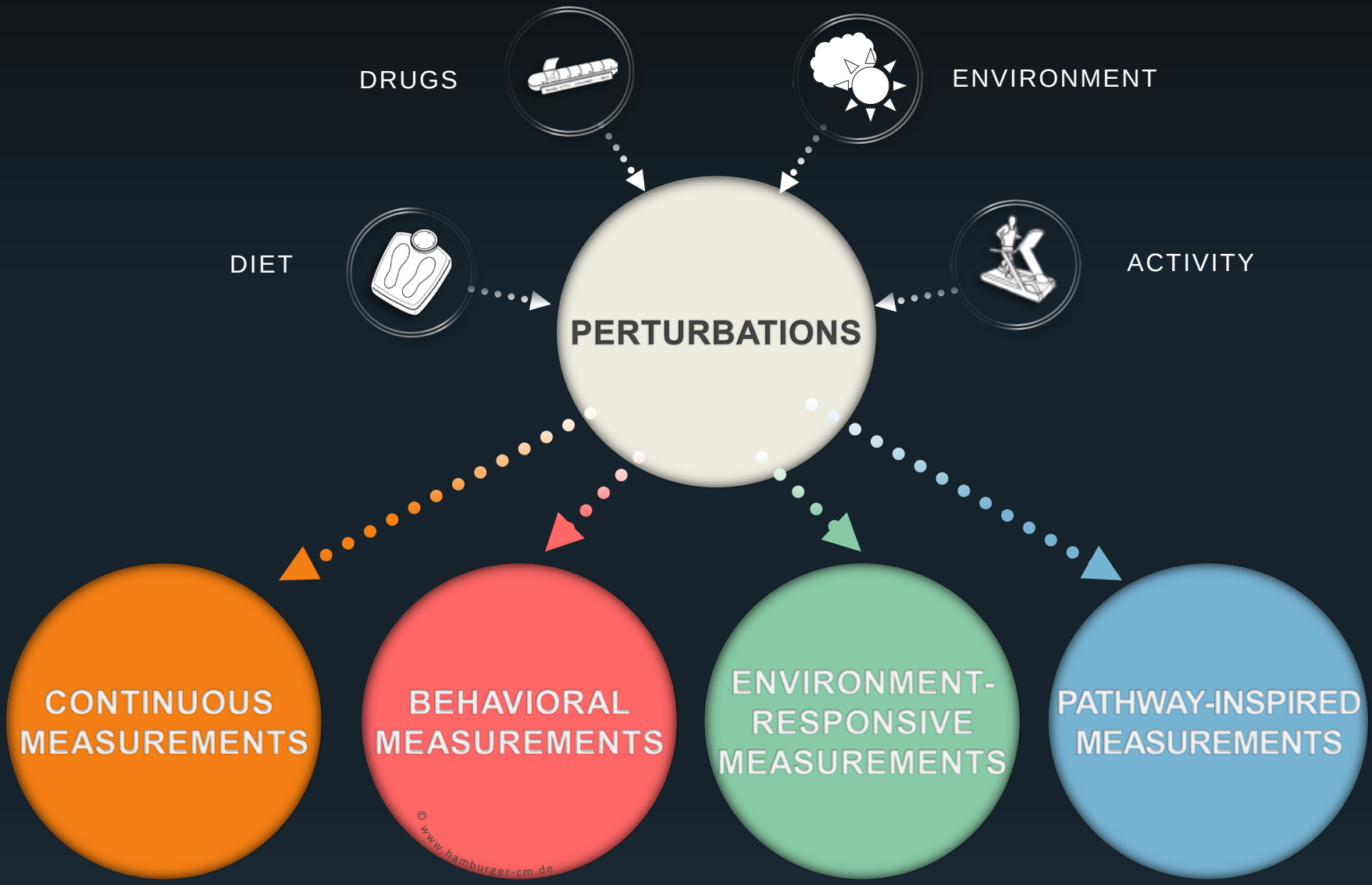


February 15, 014
Doe
9:00	

Novel phenotypes, analyzed in the context of perturbations



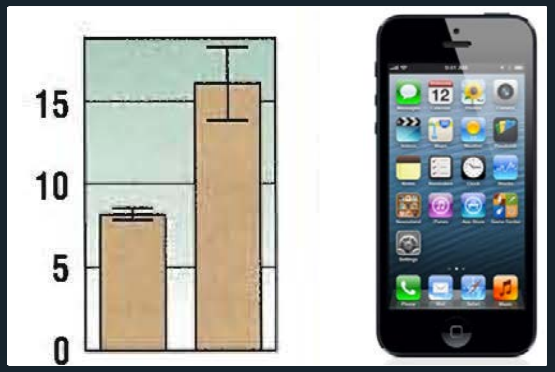
Novel phenotypes, analyzed in the context of perturbations



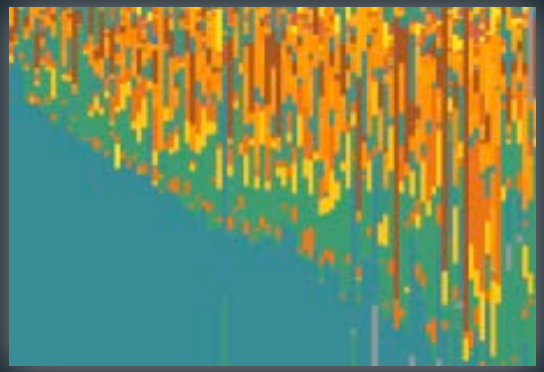
The integration of data from *different scales* and *different sources*, analyzed with a *broadening array of techniques.*

Repurposed data to yield new ideas

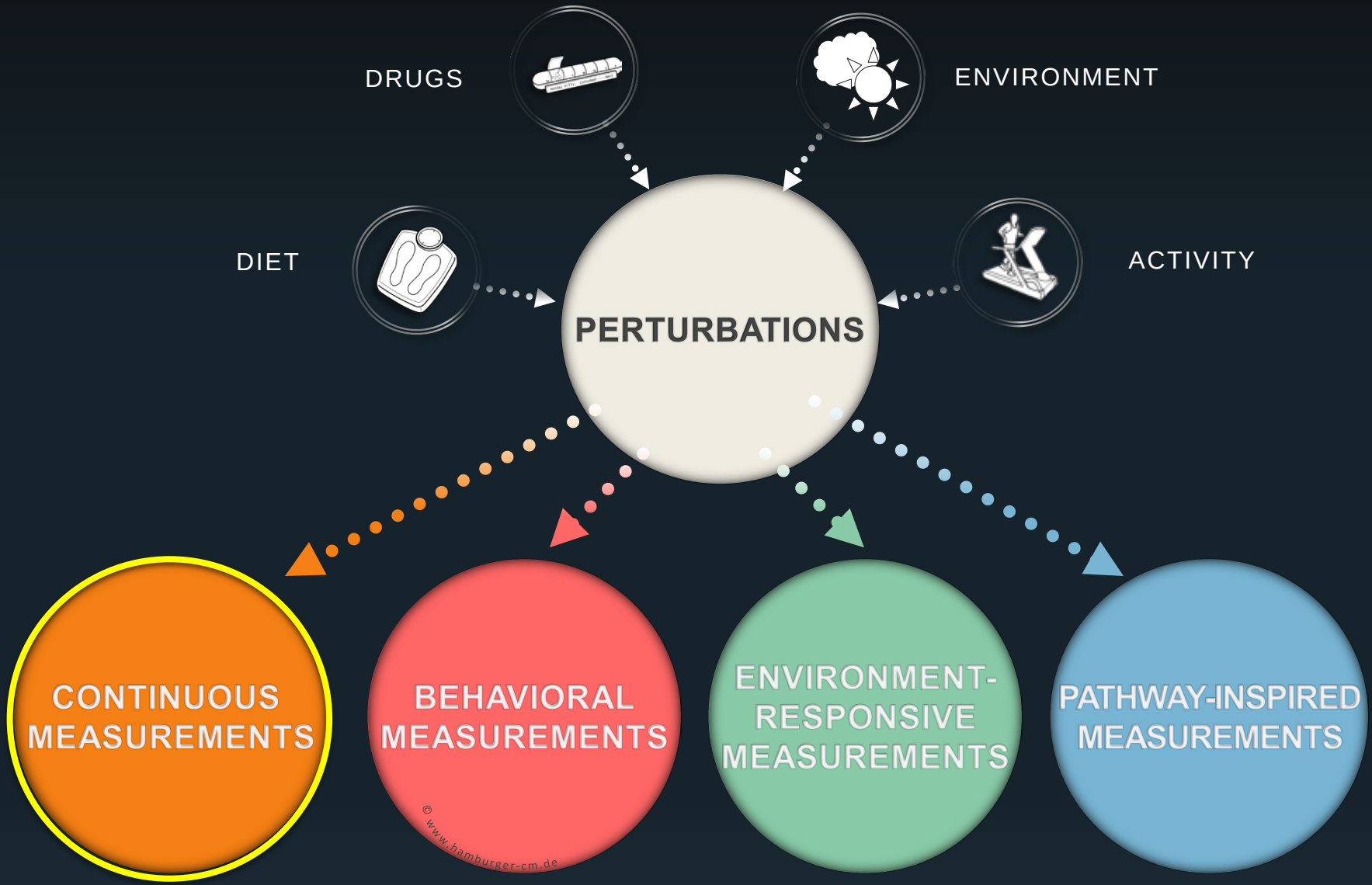
Data collected via new methods



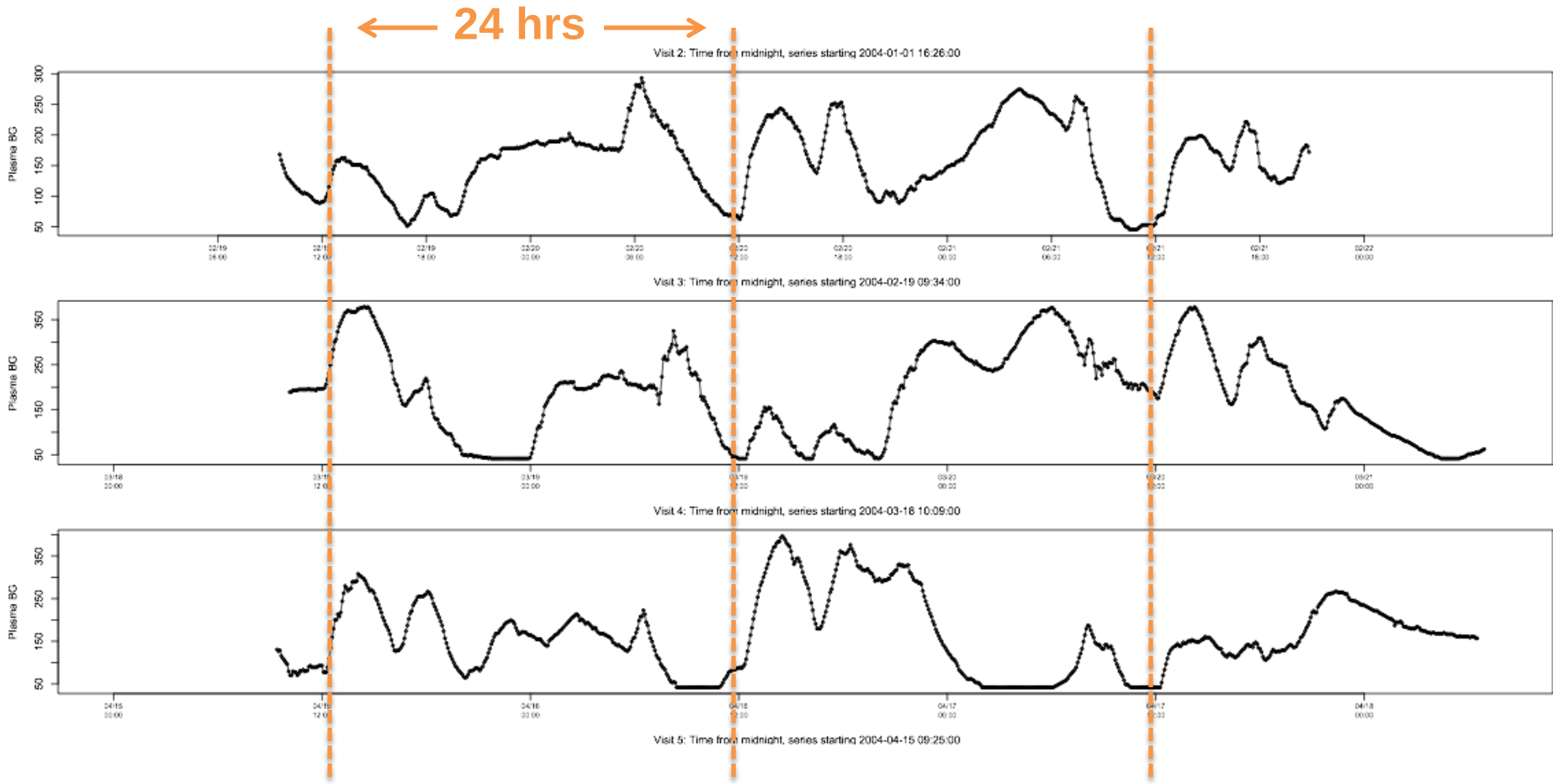
High Dimensional Data Sets



Novel phenotypes, analyzed in the context of perturbations

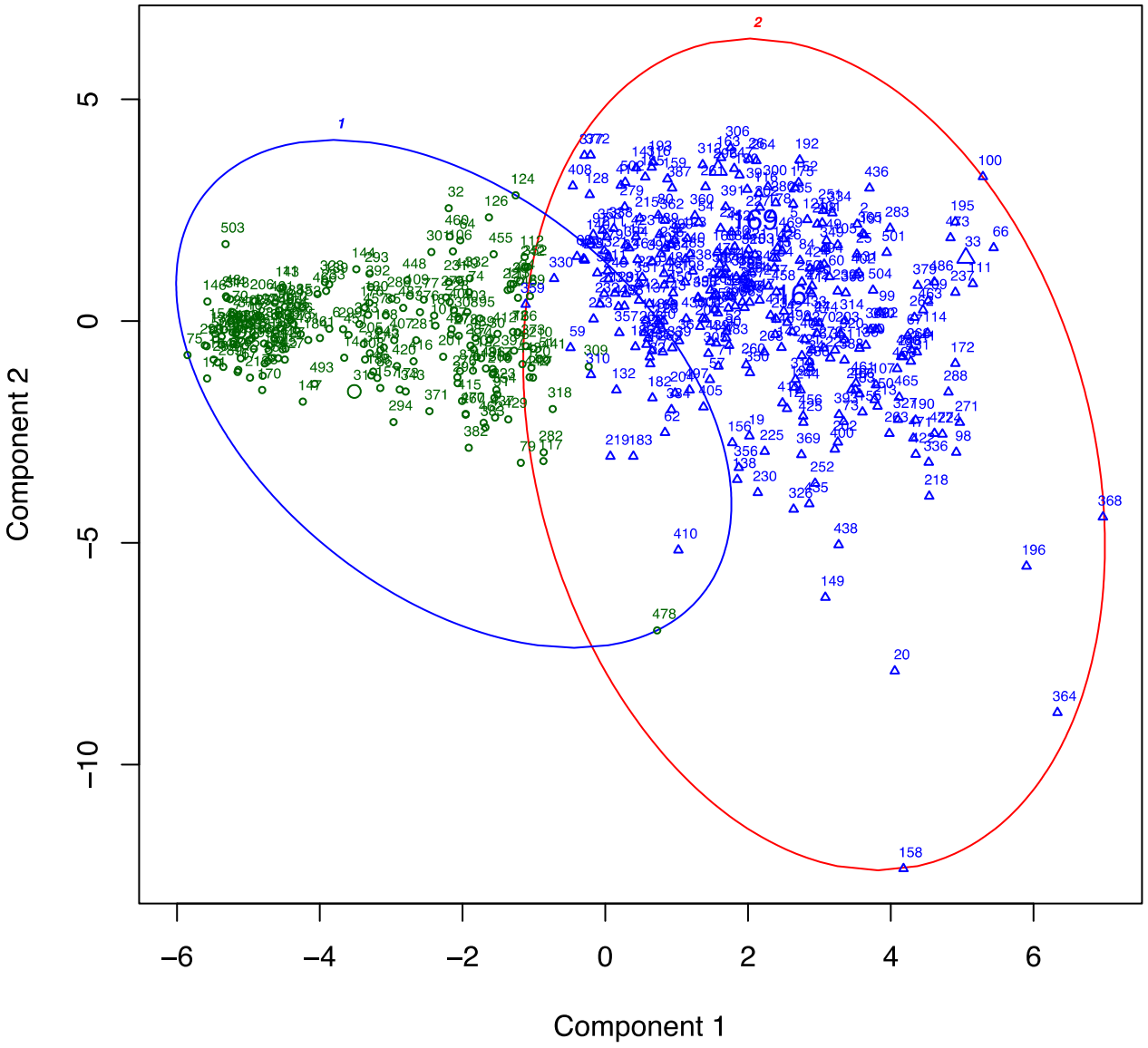


Physiologic insights from a therapeutic device: Continuous Glucose Monitoring

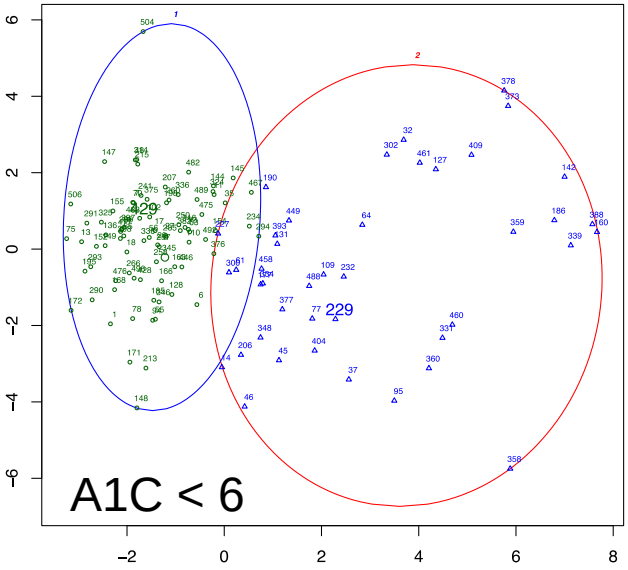


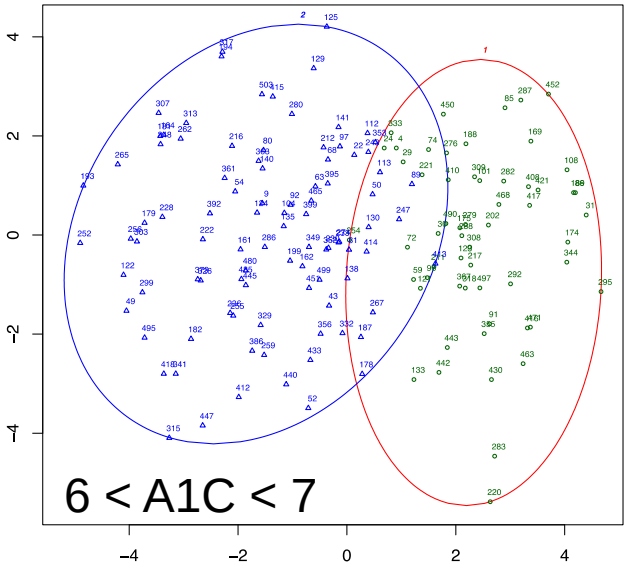
CGM data clusters participants

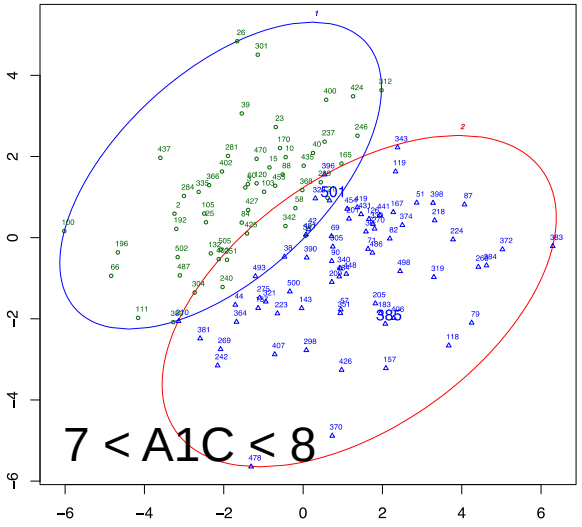
(determined by Principal Component Analysis)

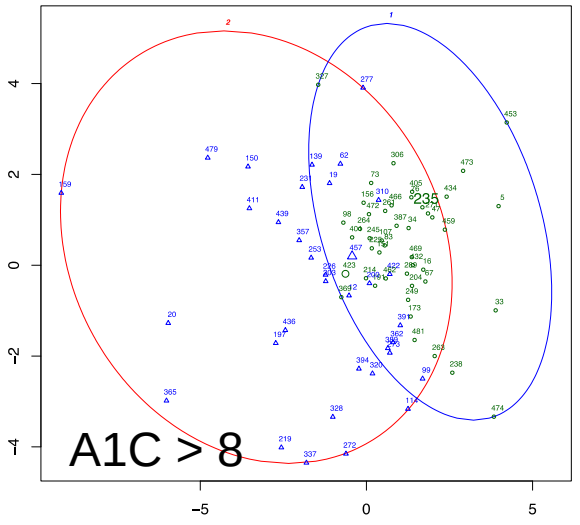


Clusters persist across diabetes status, glucose control, medication

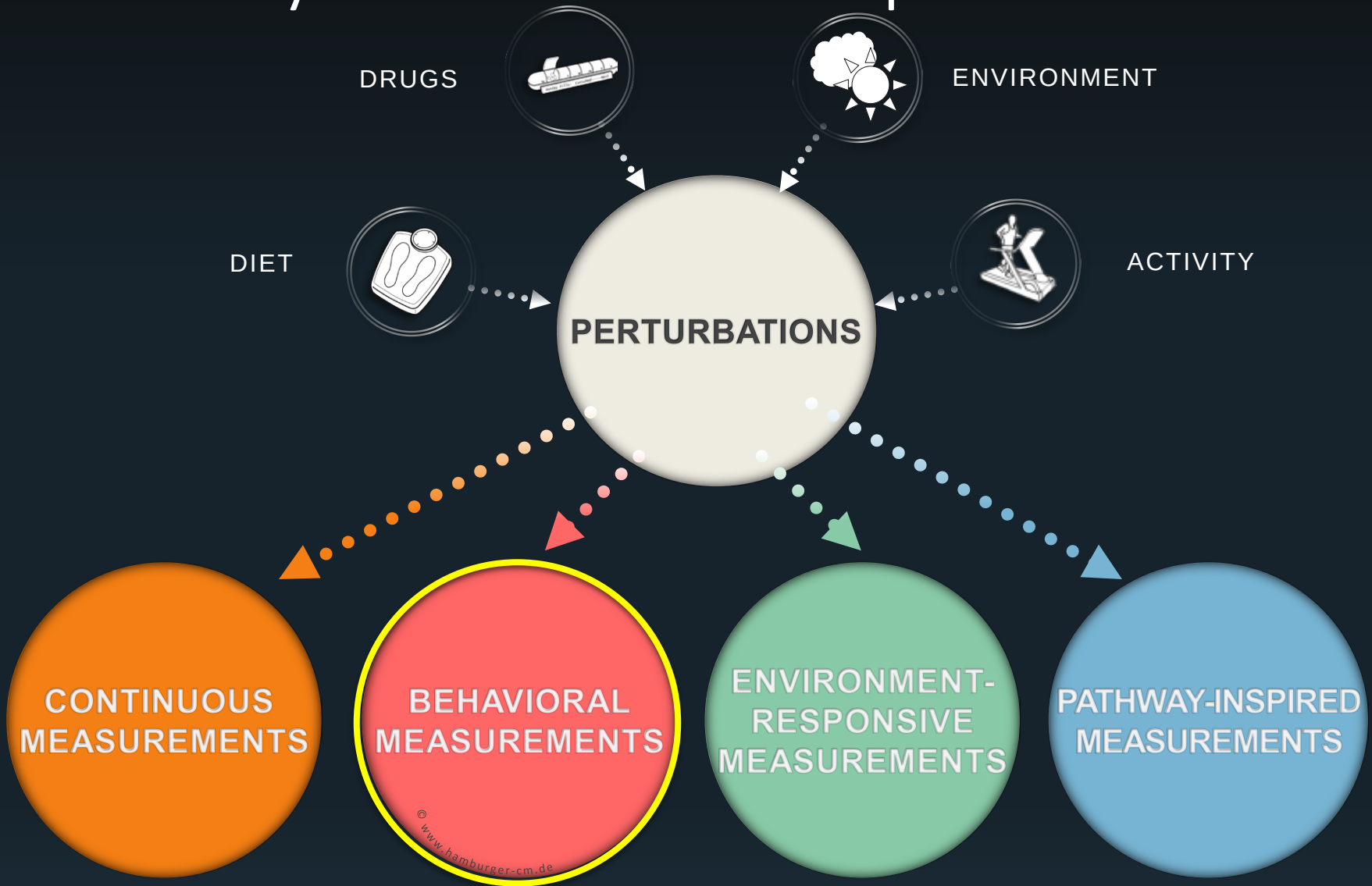








Novel phenotypes, analyzed in the context of perturbations



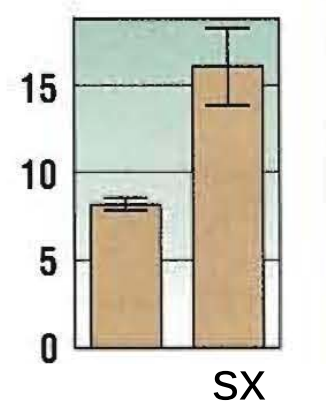
Behavioral Measurements

As we begin to assess health holistically
we need to turn again to non-traditional technology

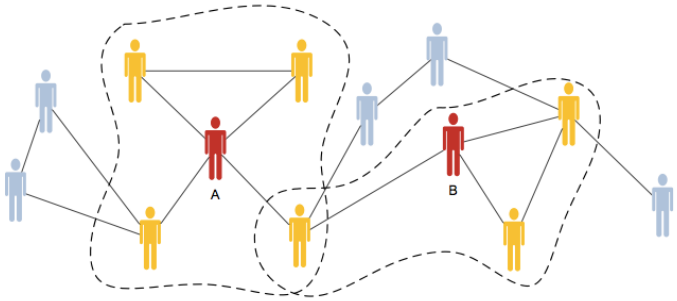
Minimally Invasive

Minimally Intrusive

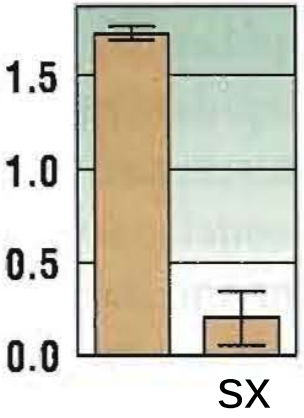
Phenotypes at home:
Passive and active behavioral analytics



Runny nose:
Late night/early morning communication



Social contacts for peer incentives:
BEHAVIOR



Fever, influenza:
WLAN ‘entropy’

Sandy Pentland (MIT Media Lab)

Phenotypes at population scale

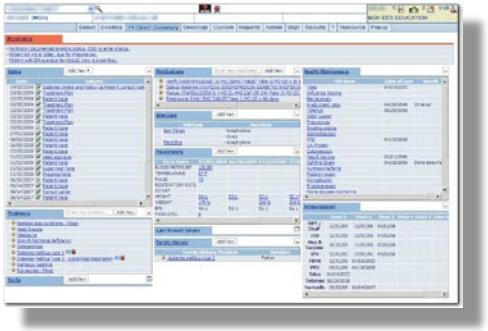
Wearable Sensors, Electronic Medical Records, biospecimens and integrated analysis for discovery

FROM RESEARCH POPULATIONS …

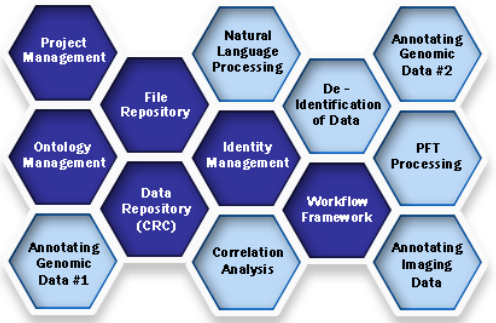
… TO “REAL-WORLD” INDIVIDUALS

EMRs to integrate research with clinical care and patient cells

Partners EMR (~4M patients)



i2b2 analysis software (phenotype extraction)



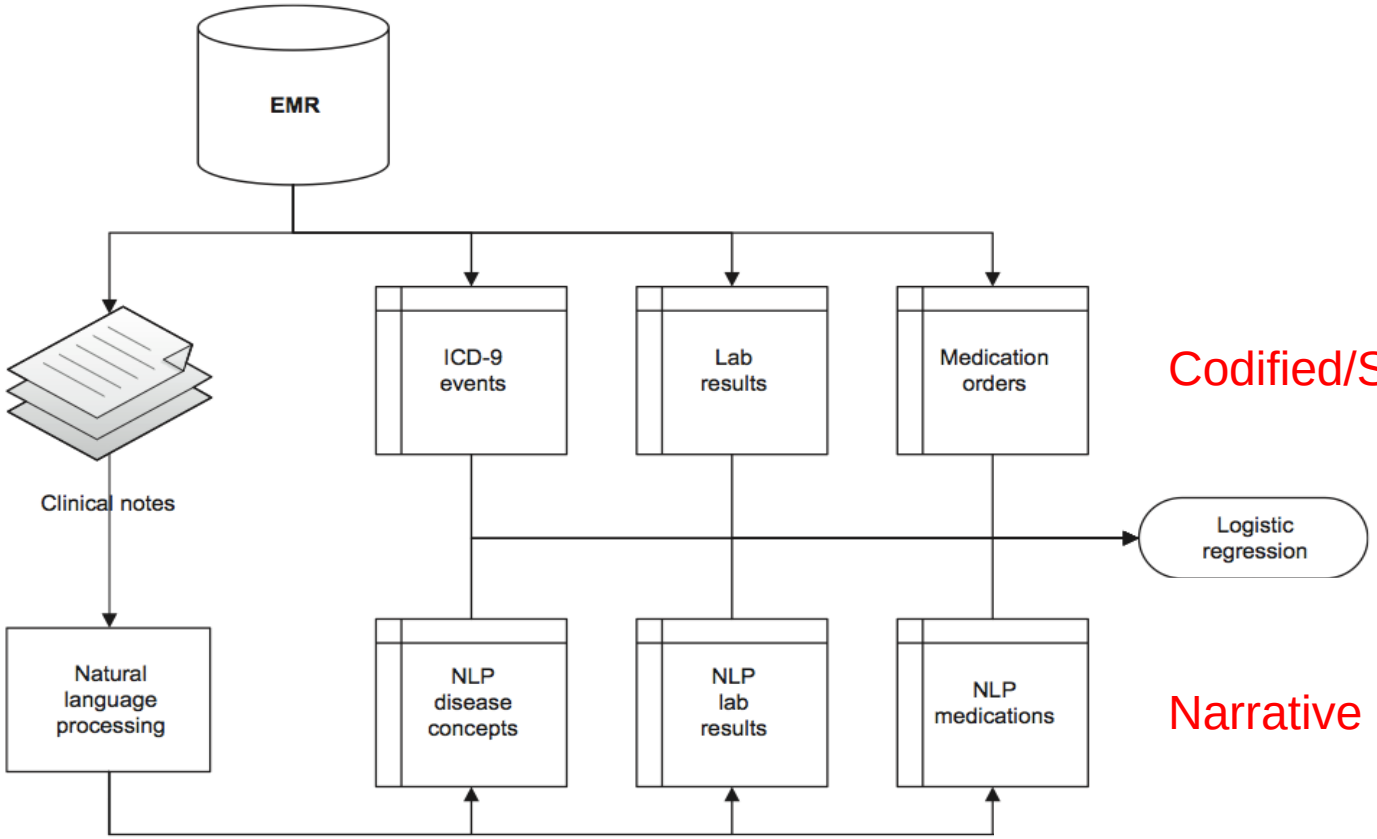
Virtual patient cohort

(De-identified)

Matched, de-identified biospecimens from clinical labs (Crimson)

Cost-effective measurement of genetic variation and phenotypes of large populations
"Real world" patients
Maintain patient privacy

Advanced phenotyping using data from routine clinical care

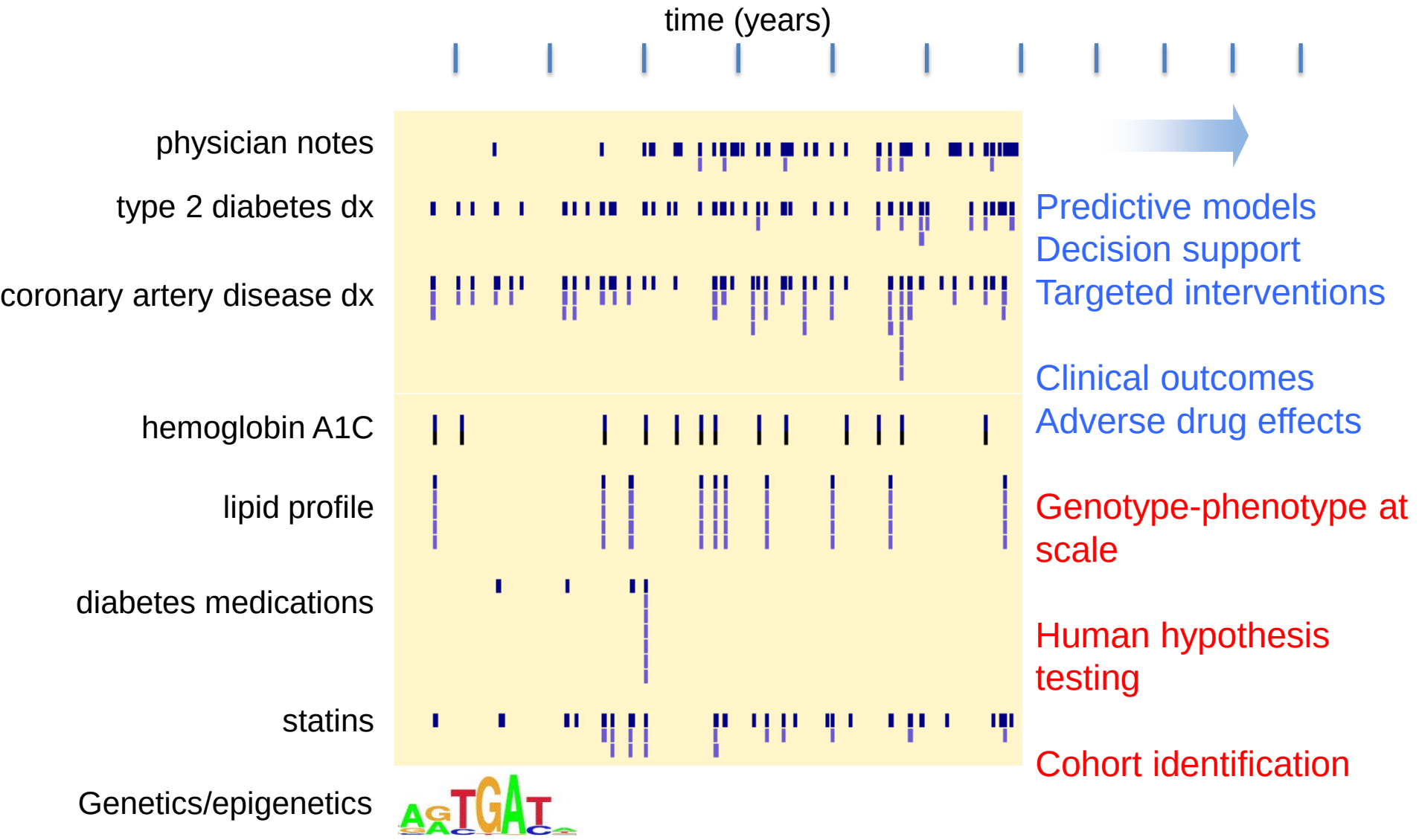


Codified/Structured Data

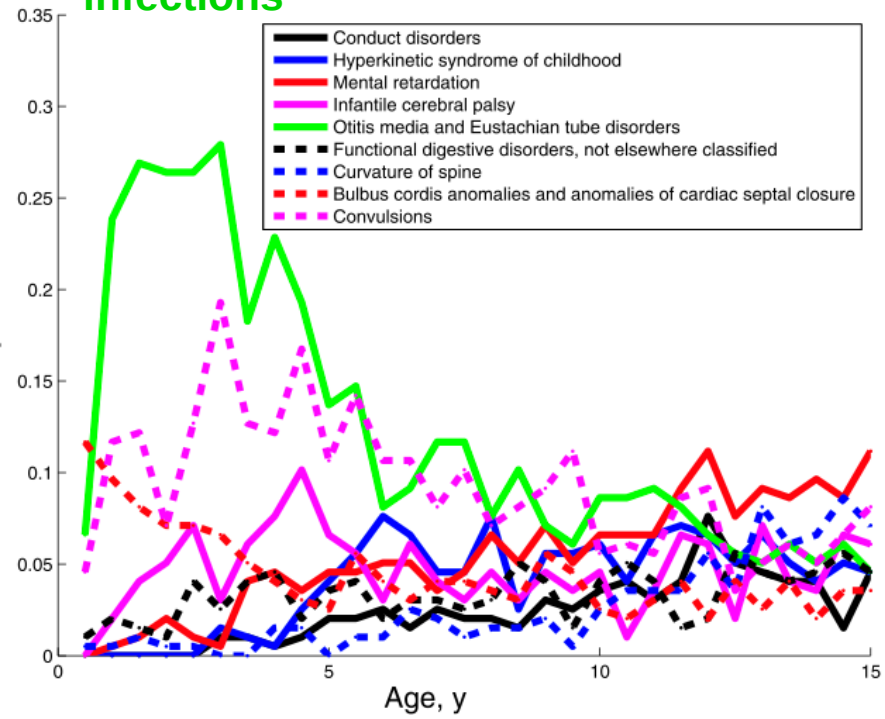
Narrative Data

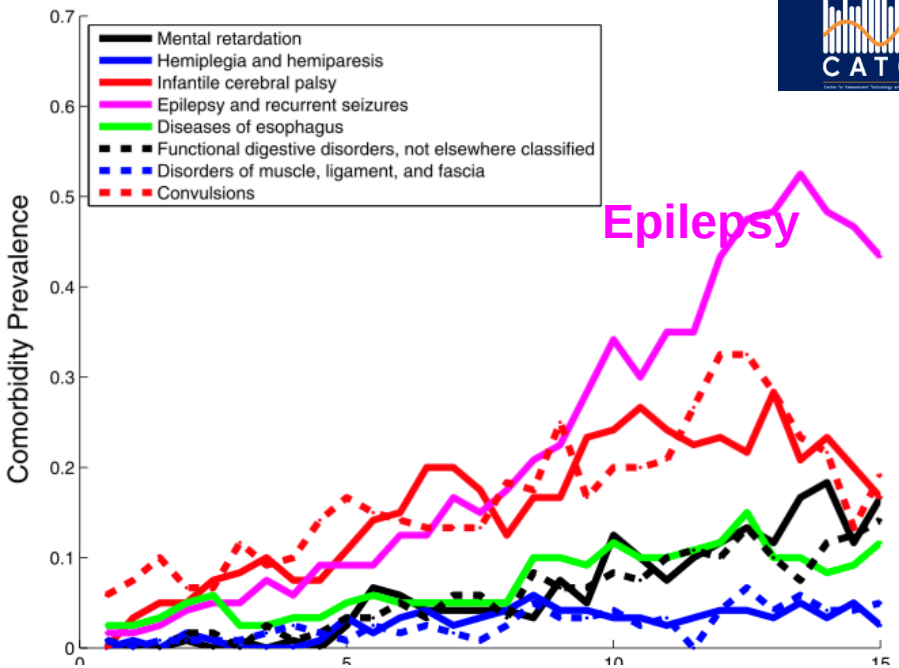
Carroll et al., JAMIA 2012;19:e162

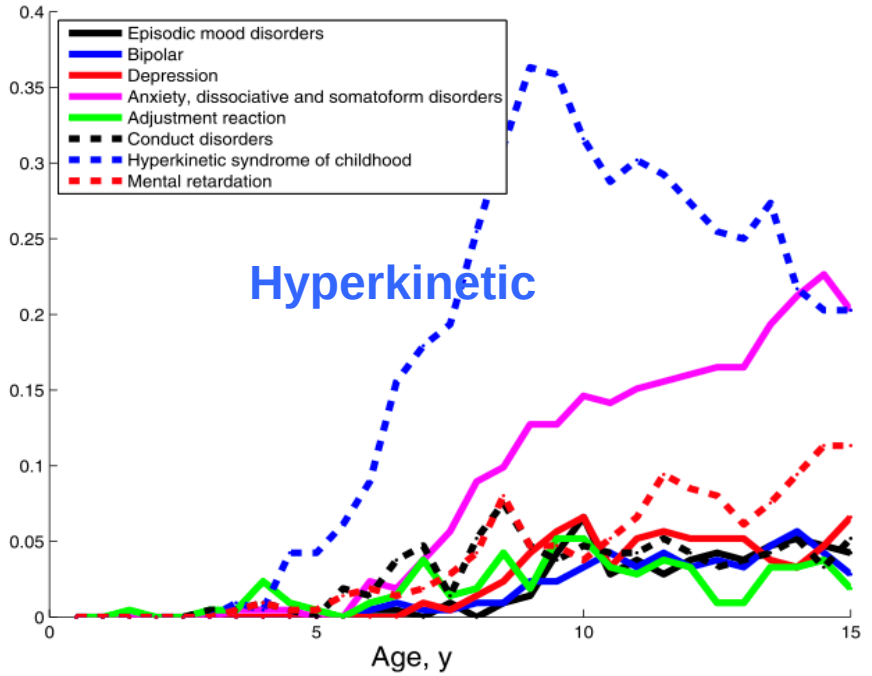
Towards predictive models for outcomes



Stratifying natural history of autism via EMR





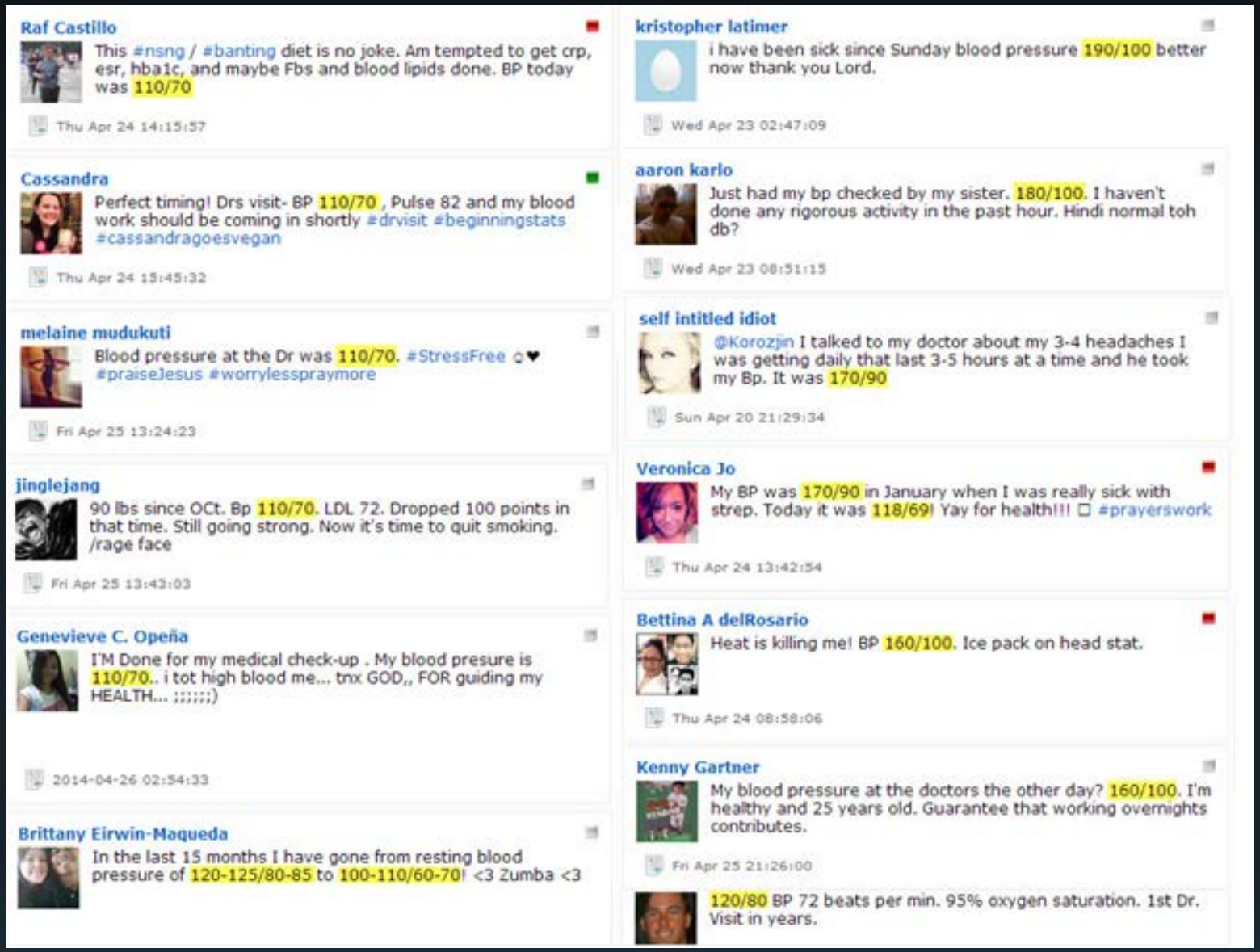


Kohane and colleagues Pediatrics (2014)

We have the genetic and digital revolutions helping to guide health.

What about the power of social media?

Moving from social media and tweets …. to Health!



Raf Castillo

This #nsng / #banting diet is no joke. Am tempted to get crp, esr, hba1c, and maybe Fbs and blood lipids done. BP today was 110/70

Thu Apr 24 14:15:57

Cassandra

Perfect timing! Drs visit- BP 110/70 , Pulse 82 and my blood work should be coming in shortly #drvisit #beginningstats #cassandragoesvegan

Thu Apr 24 15:45:32

melaine mudukuti

Blood pressure at the Dr was 110/70. #StressFree ☺❤ #praiseJesus #worrylesspraymore

Fri Apr 25 13:24:23

jinglejang

90 lbs since OCt. Bp 110/70. LDL 72. Dropped 100 points in that time. Still going strong. Now it's time to quit smoking. /rage face

Fri Apr 25 13:43:03

Genevieve C. Opeña

I'M Done for my medical check-up . My blood presure is 110/70.. i tot high blood me... tnx GOD,, FOR guiding my HEALTH... ;;;;;;)

2014-04-26 02:54:33

Brittany Eirwin-Maqueda

In the last 15 months I have gone from resting blood pressure of 120-125/80-85 to 100-110/60-70! <3 Zumba <3

kristopher latimer

i have been sick since Sunday blood pressure 190/100 better now thank you Lord.

Wed Apr 23 02:47:09

aaron karlo

Just had my bp checked by my sister. 180/100. I haven't done any rigorous activity in the past hour. Hindi normal toh db?

Wed Apr 23 08:51:15

self intitled idiot

@Korozjin I talked to my doctor about my 3-4 headaches I was getting daily that last 3-5 hours at a time and he took my Bp. It was 170/90

Sun Apr 20 21:29:34

Veronica Jo

My BP was 170/90 in January when I was really sick with strep. Today it was 118/69! Yay for health!!! ☐ #prayerswork

Thu Apr 24 13:42:54

Bettina A delRosario

Heat is killing me! BP 160/100. Ice pack on head stat.

Thu Apr 24 08:58:06

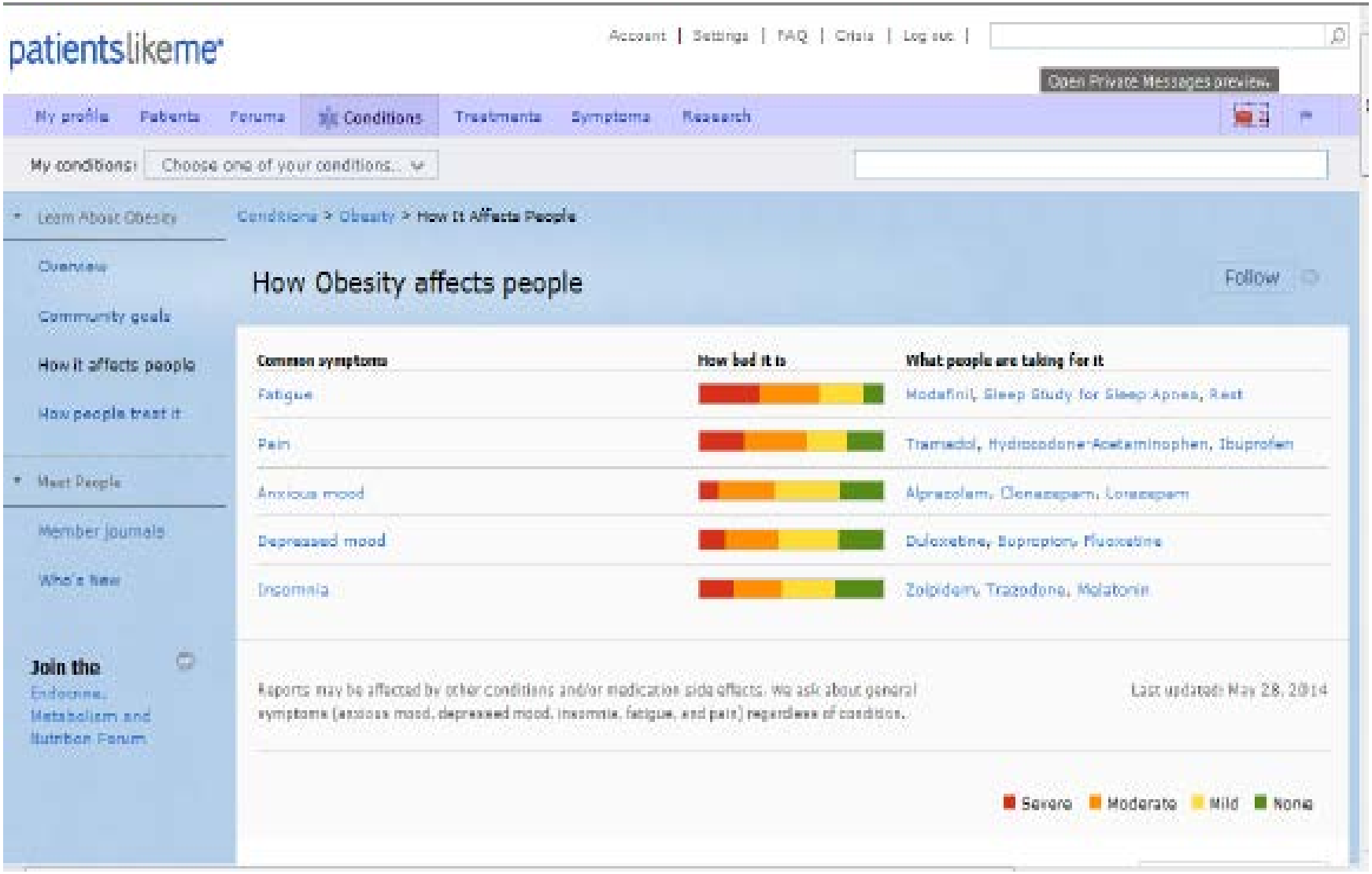
Kenny Gartner

My blood pressure at the doctors the other day? 160/100. I'm healthy and 25 years old. Guarantee that working overnights contributes.

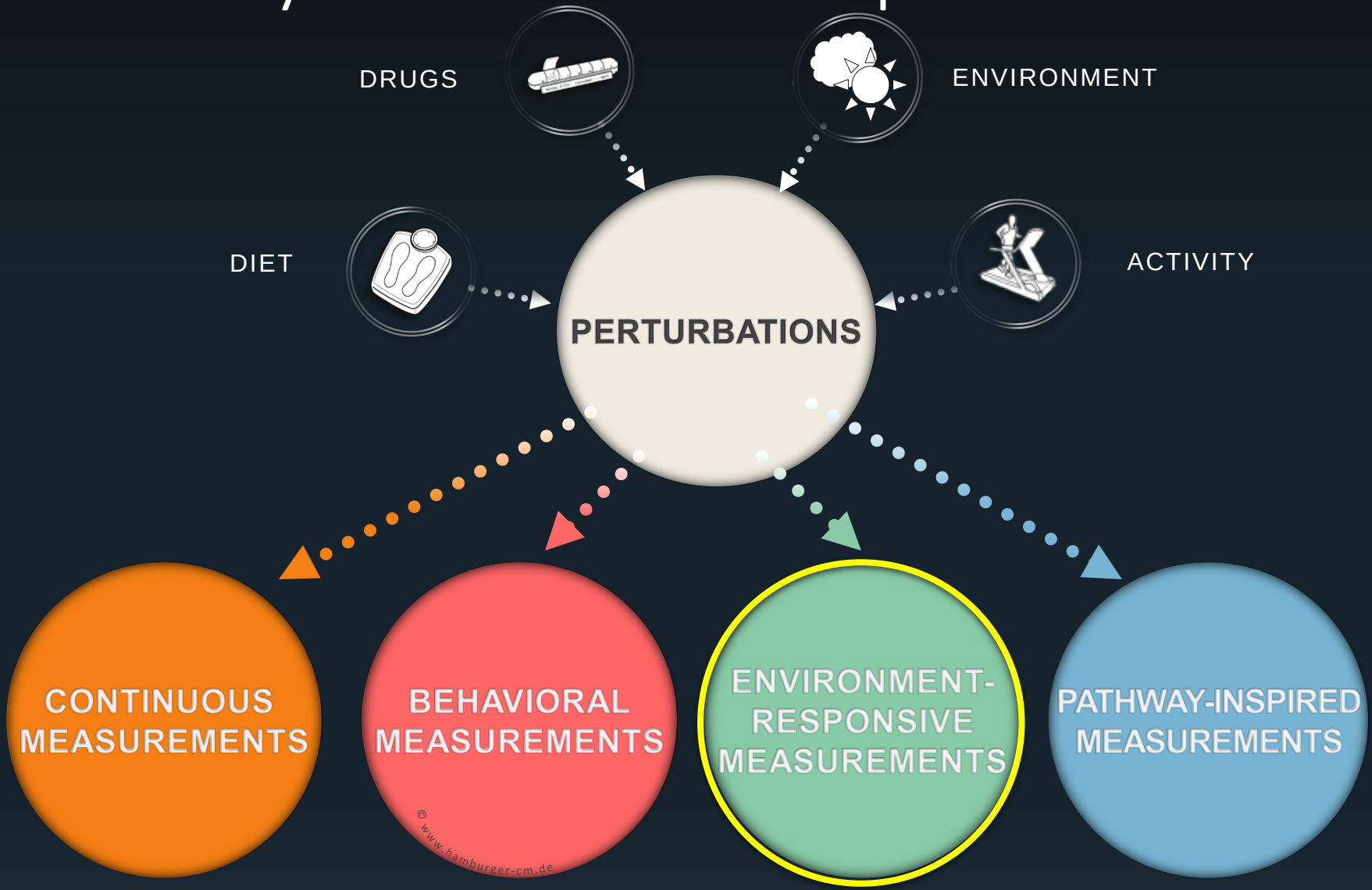
Fri Apr 25 21:26:00

120/80 BP 72 beats per min. 95% oxygen saturation. 1st Dr. Visit in years.

Social Media for Healthcare has already arrived with patientslikeme®



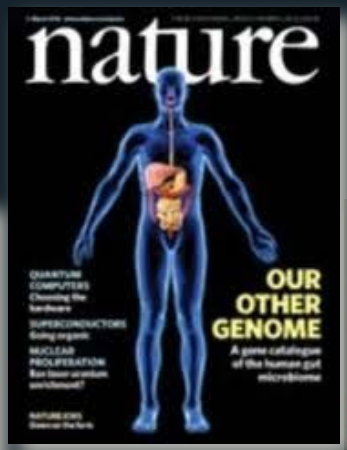
Novel phenotypes, analyzed in the context of perturbations



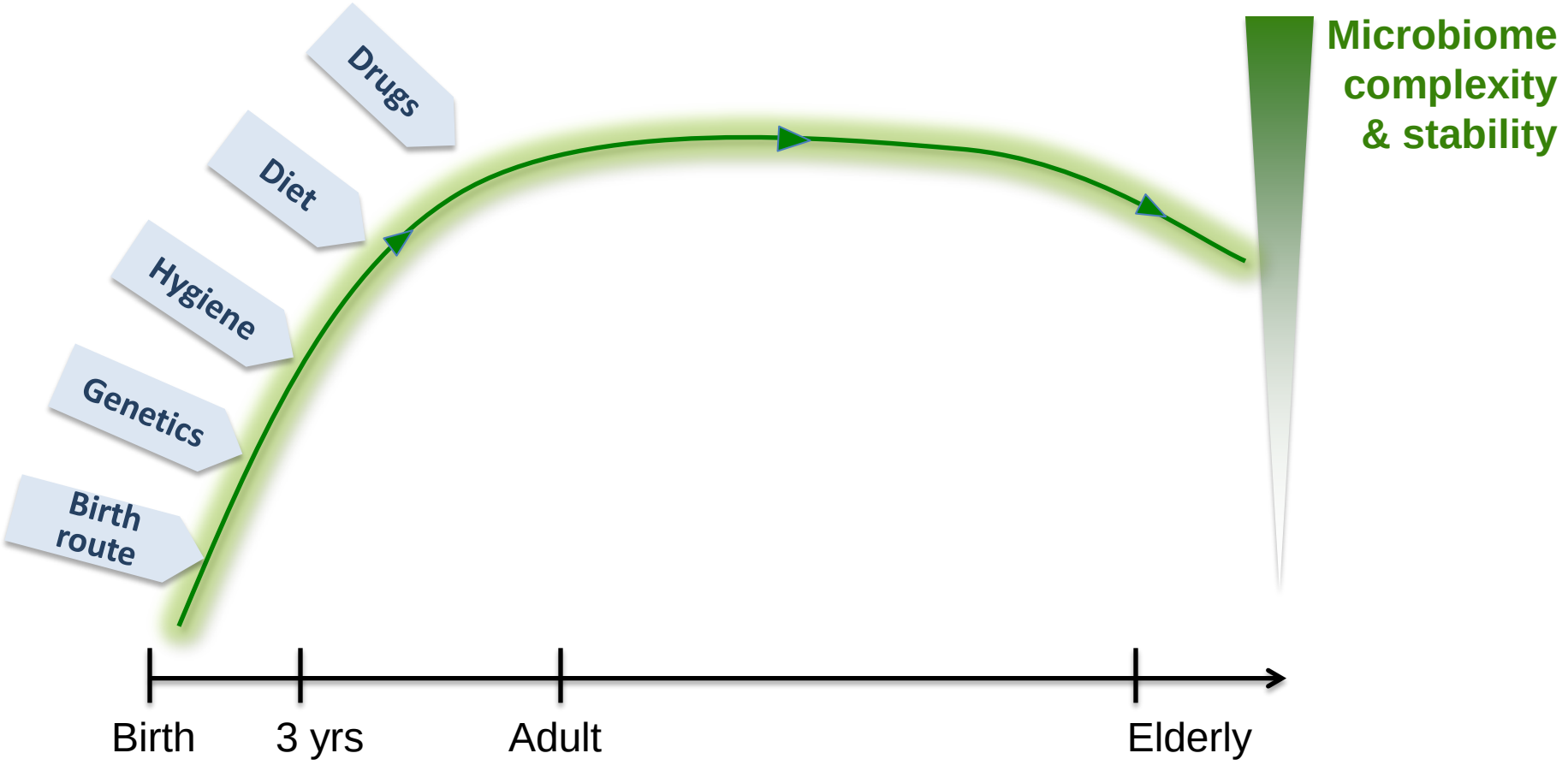
The Human Microbiome

What we know about them:

- Microbes outnumber human cells **10 to 1**
- They collectively hold **8 million** unique genes
- There are **10,000** species of microbes
- You carry **2 - 6 lbs** of bacteria

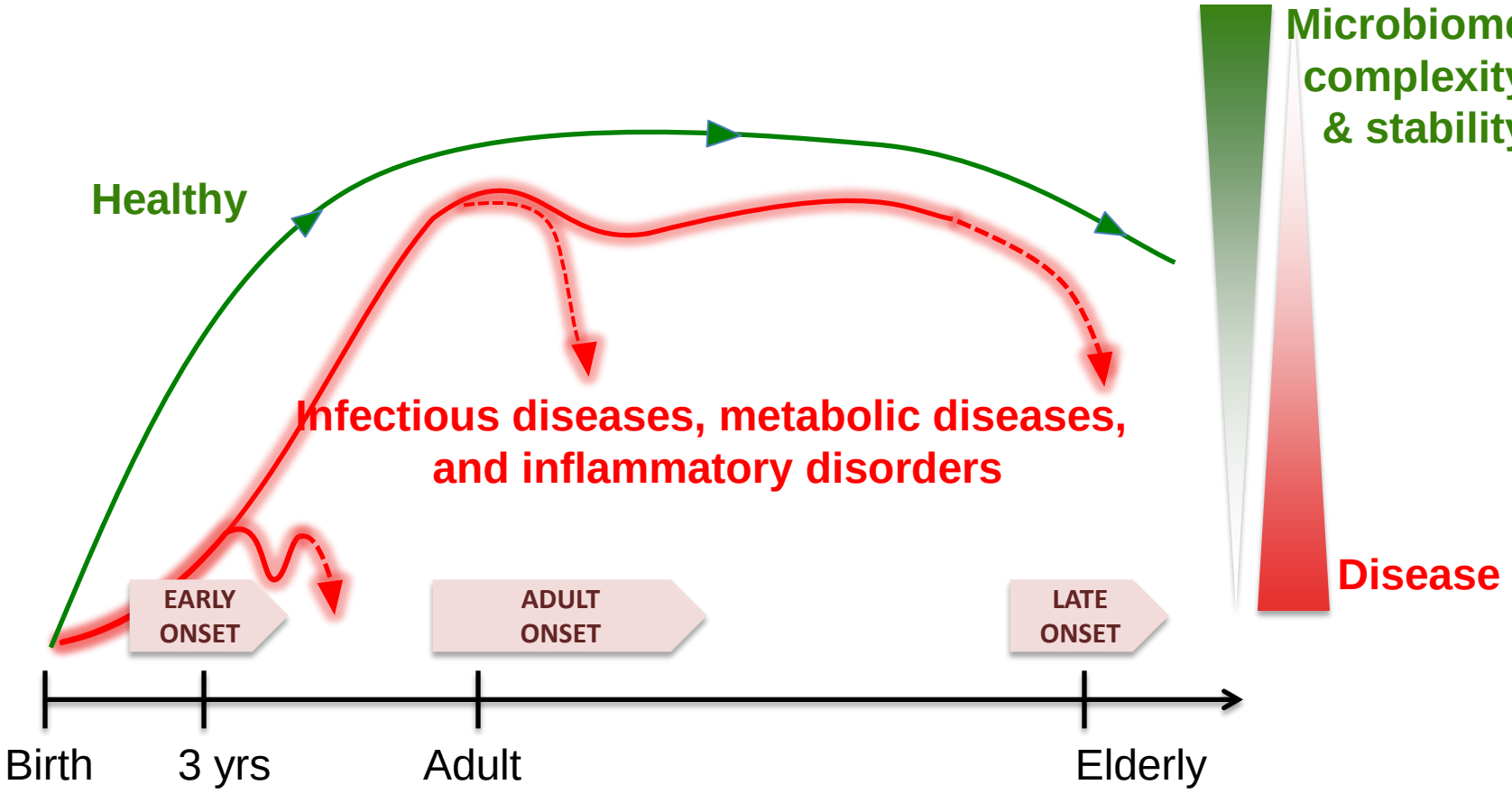


A healthy microbiome *in* a healthy body



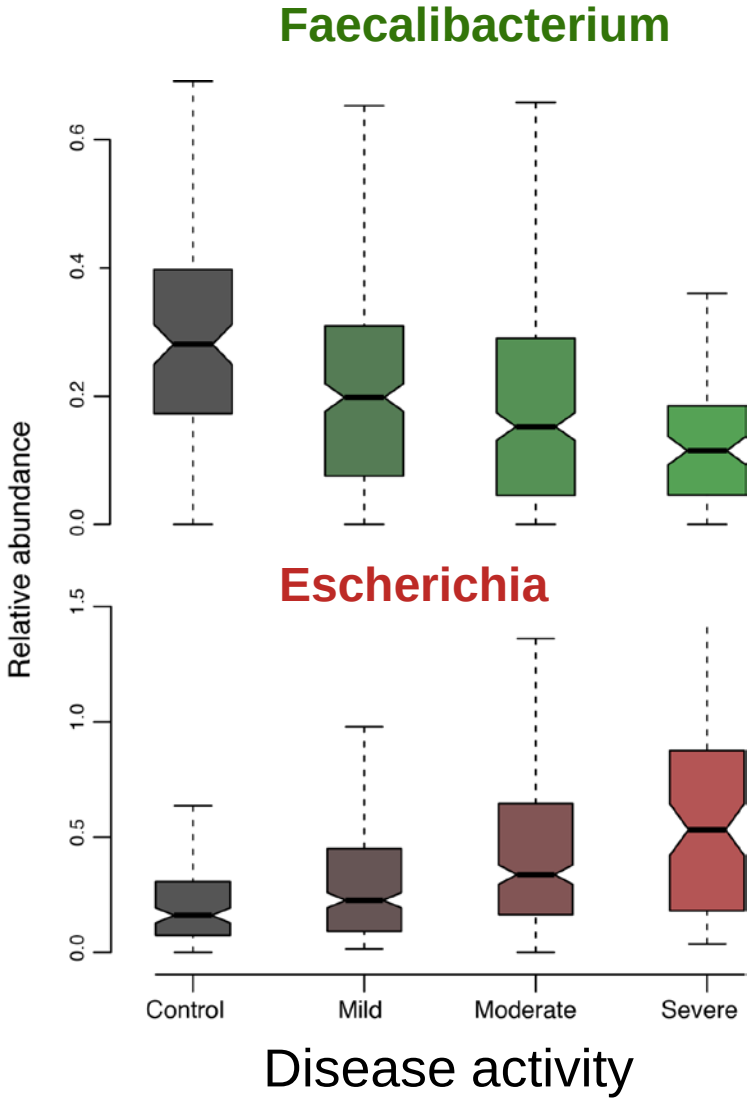
Genetics and environmental factors contribute to the development of the microbiome

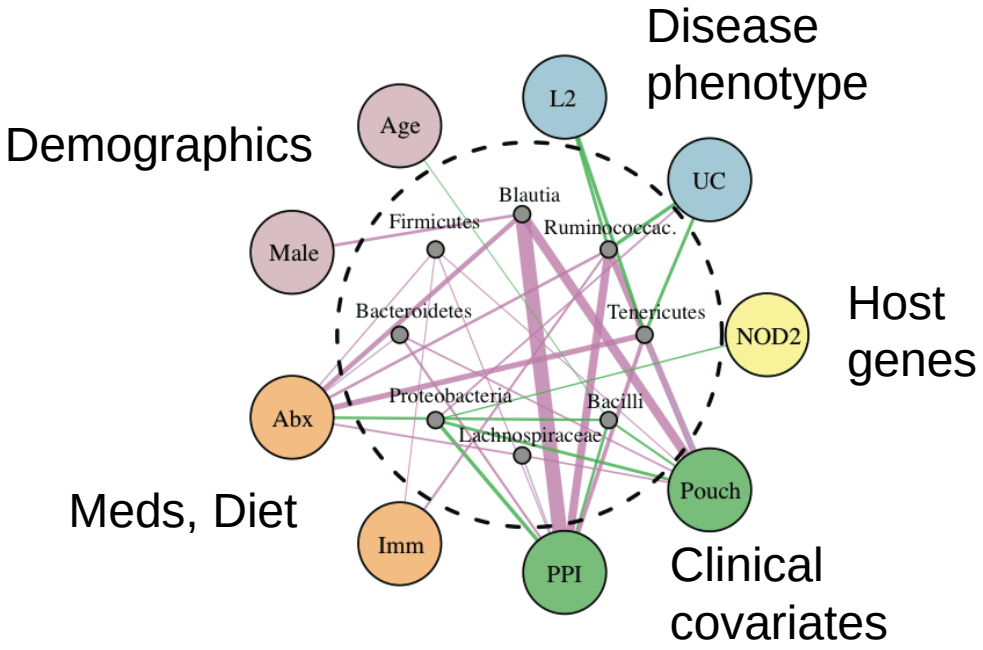
Dysbiosis is implicated in diseases



Opportunity to use this information to diagnose, predict, and treat diseases

Microbiome interacts with host genome, environment, disease phenotypes



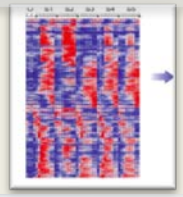


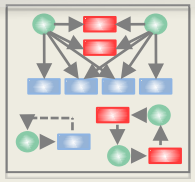
Knights, Xavier, Gevers, Huttenhower

Integrating phenotypes at many levels: chronic diseases with periodic flares

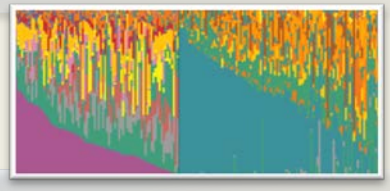
days

Blood samples

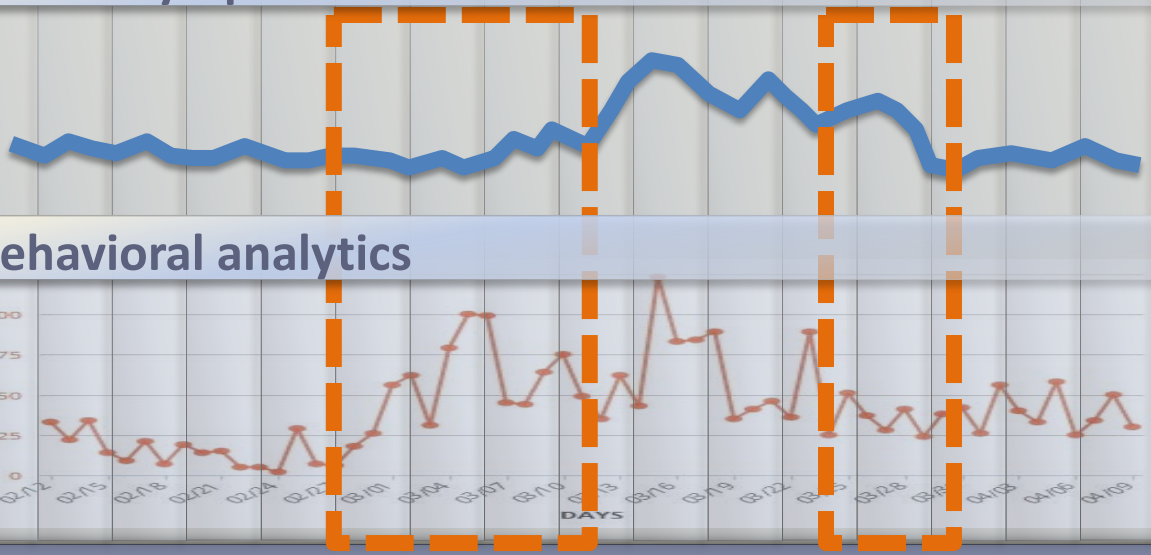




Stool samples



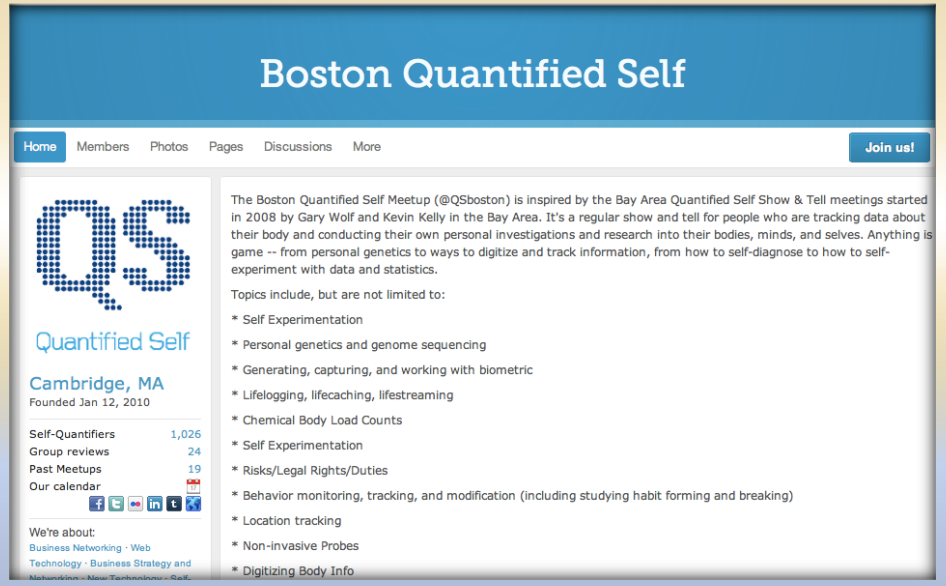
Patient symptoms



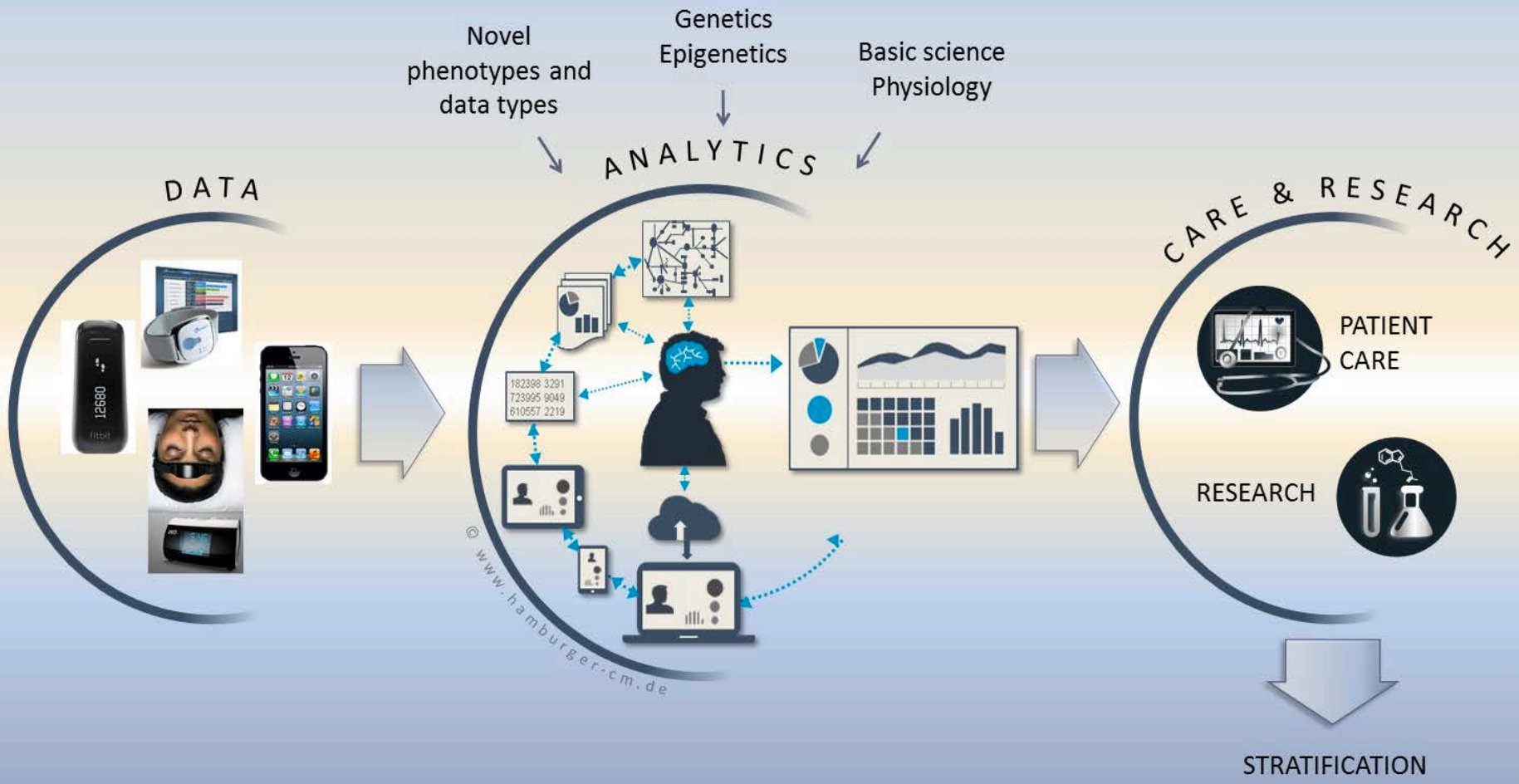
Behavioral analytics

GINGER.io

An ecosystem outside of medicine



An ecosystem outside of medicine



A new partnership with patients

Engaged, participatory

Two-way information and learning exchange

Patient-controlled data

Unify wellness with spirit of inquiry

Convergence of multiple disciplines