Personalized Medicine

Something old, something new and a systems view

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Department of Surgery, *Rutgers-RWJ Medical School*

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1766-2016 RUTGERS 250 *Revolutionary for 250 Years*

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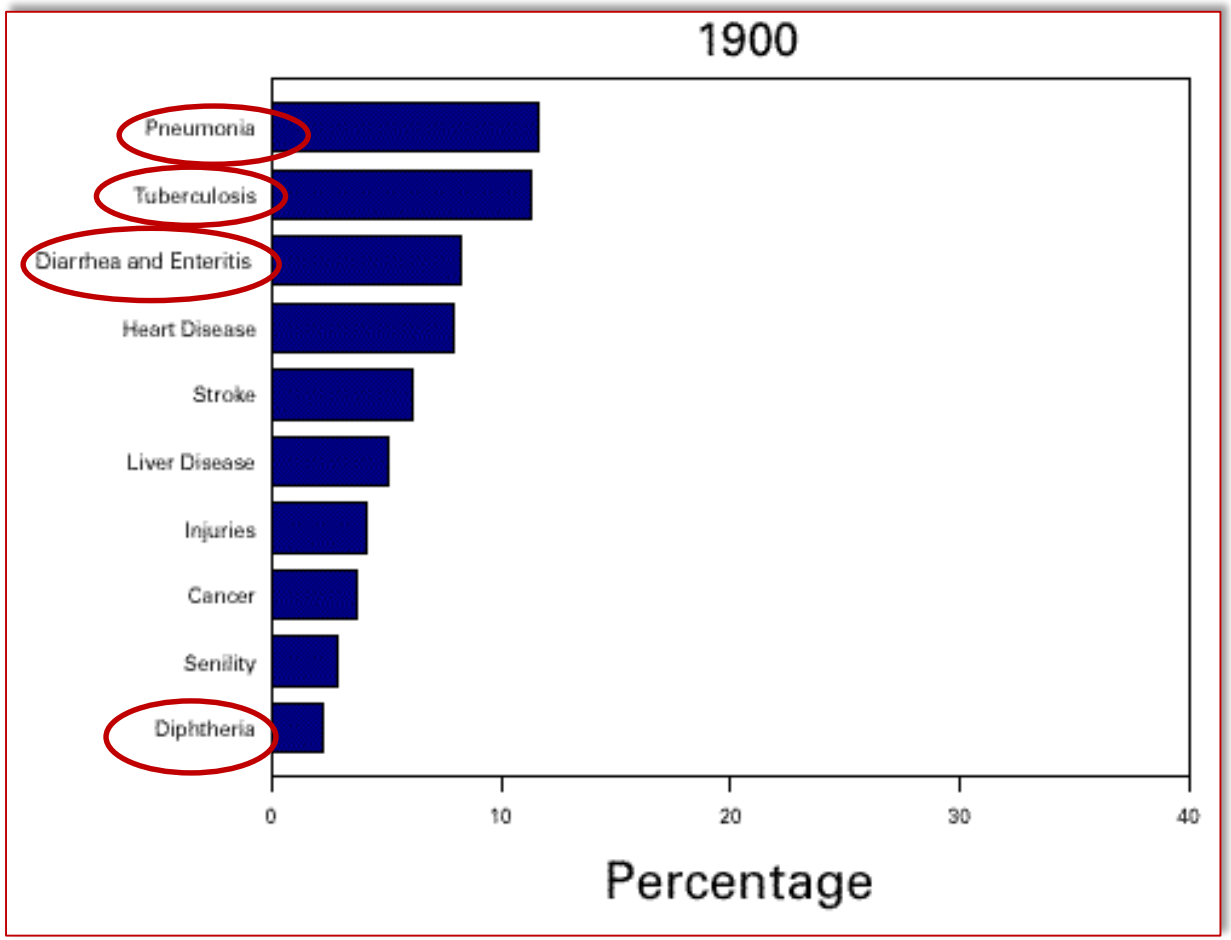
In case I loose you

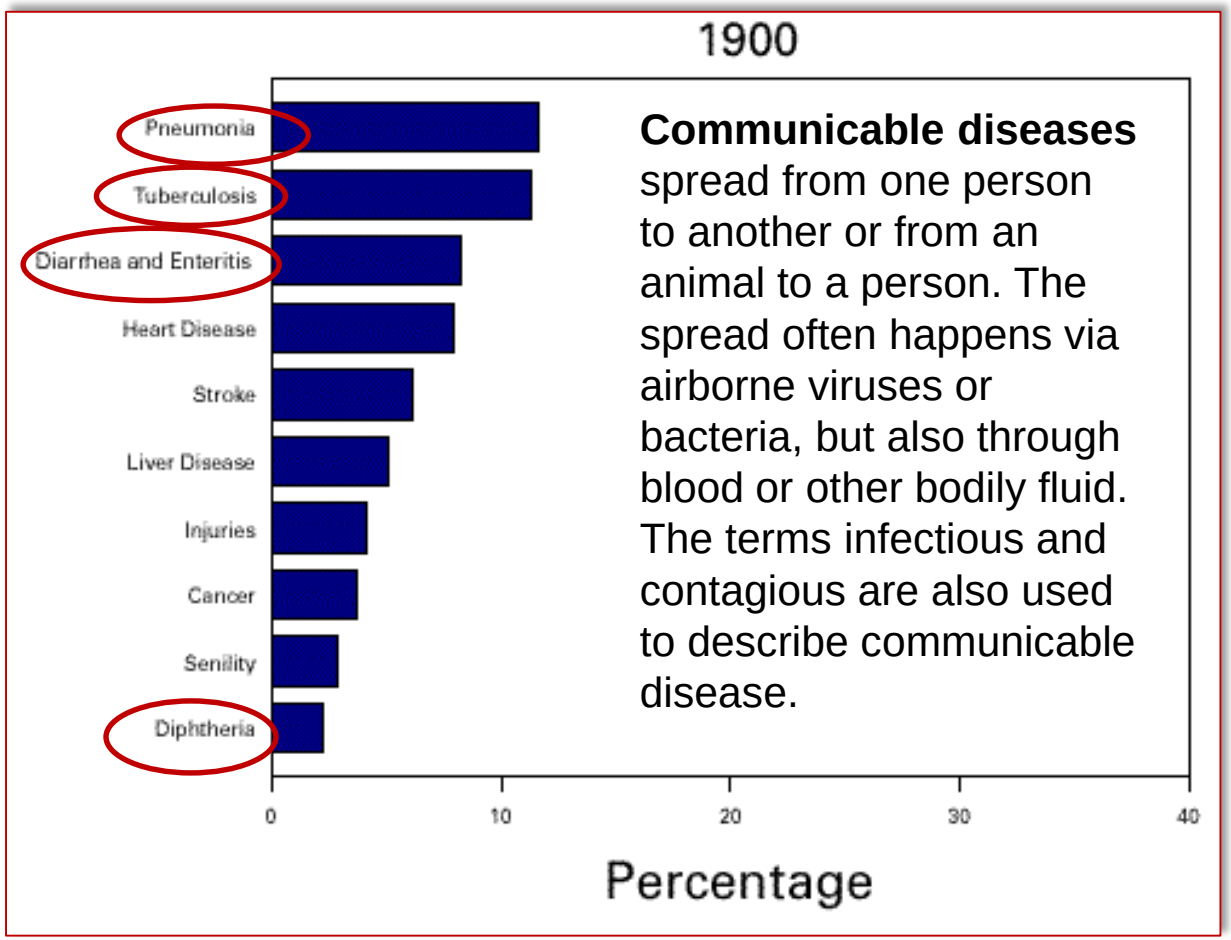
What I would like to discuss is: *should we personalize the treatment or the ~~patient~~ individual ?*

Leading causes of death in the USA in the early 1900's



https://www.cdc.gov/mmwr/preview/mmwrhtml/mm4829a1.htm

Leading causes of death in the USA in the early 1900's



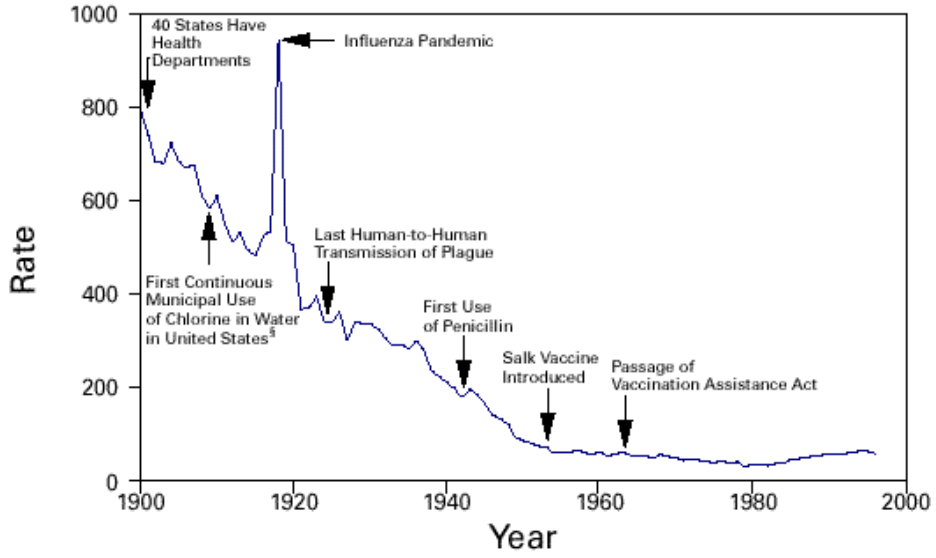
Communicable diseases spread from one person to another or from an animal to a person. The spread often happens via airborne viruses or bacteria, but also through blood or other bodily fluid. The terms infectious and contagious are also used to describe communicable disease.

https://www.cdc.gov/mmwr/preview/mmwrhtml/mm4829a1.htm

Infectious diseases and the *germ theory of disease*

"bad air from swampy areas" (*Hippocrates, 460 BC)*

The germ theory is a fundamental tenet of medicine stating that microorganisms invade the body and cause certain diseases. One must be able to isolate and eliminate the microbe from the patient.

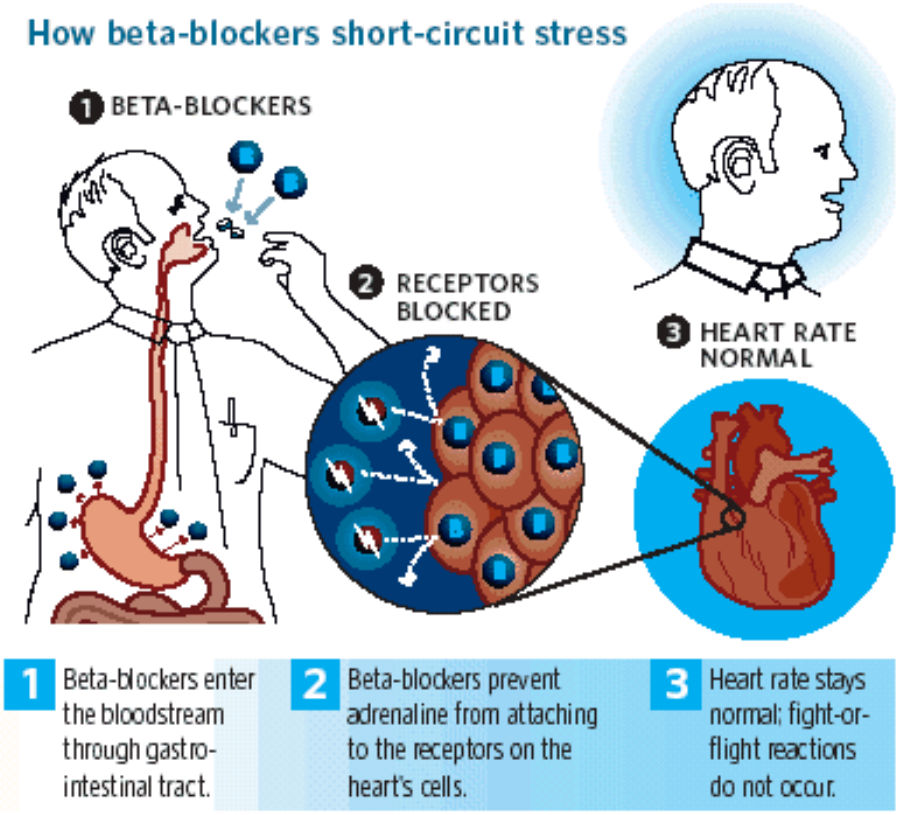


*Per 100,000 population per year.
†Adapted from Armstrong GL, Conn LA, Pinner RW. Trends in infectious disease mortality in the United States during the 20th century. JAMA 1999:281;61–6.
§American Water Works Association. Water chlorination principles and practices: AWWA manual M20. Denver, Colorado: American Water Works Association, 1973.

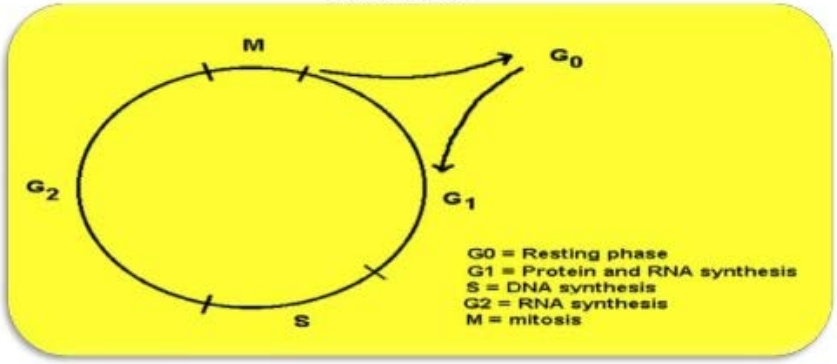
The germ theory: a fundamental concept

(I think) It defined the approach to disease treatment

Reductionist approach aimed at isolating cause/effect relations: Target the cause to eliminate the effect (symptom)



General Principles in chemotherapy of cancer



– cell cycle specific kill only actively dividing cells.

- G1: Vinblastine
- S: Mtx, cytarabine, fludarabine, G-TG, 6-MP, 5-FU, hydroxyurea, mitomycin C, doxorubicin, daunorubicin
- G2: Daunorubicin, bleomycin, etoposide, topotecan
- M: Vincristine, vinblastine, vinorelbine, paclitaxel, docetaxel

(most) Drugs *act on mechanisms driving the symptoms*

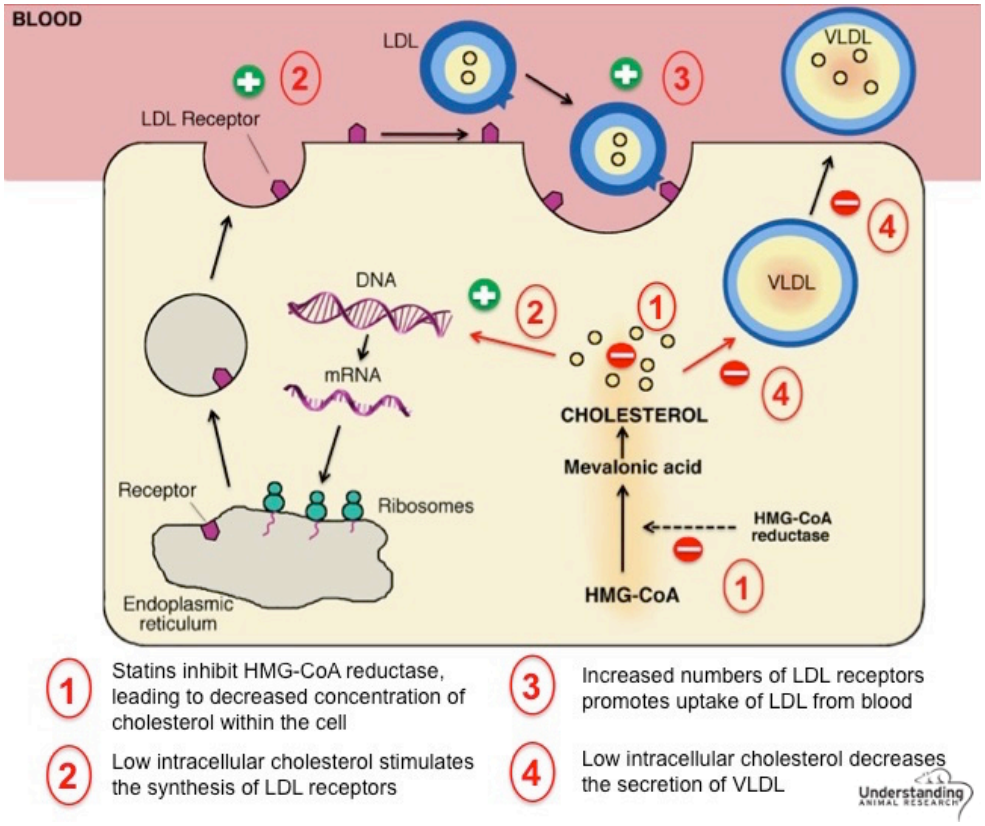
US Preventive Services Task Force Statins Recommendation Statement

Population	Adults aged 40–75 y with no history of CVD, ≥1 CVD risk factors, and calculated 10-y CVD event risk ≥10%
Recommendation	Initiate use of low- to moderate-dose statins. Grade: B

Population	Adults aged 40–75 y with no history of CVD, ≥1 CVD risk factors, and calculated 10-y CVD event risk of 7.5%–10%
Recommendatior	Discuss with patient and selectively offer use of low- to moderate-dose statins. Grade: C

Population	Adults 76 y and older with no history of CVD
Recommendation	No recommendation. Grade: I (insufficient evidence)

JAMA. 2016;316(19):1997-2007



http://www.animalresearch.info/en/drug-development/drug-prescriptions/simvastatin/

Are cause/effect relations patient-independent ?
Is the PK/PD patient-independent ?

Some things we know are not universal

Antiretroviral PK Profile: A Review of Sex Differences

	AUC/kg ♀	♂
Ritinovir	273	138
Saqumovir	34.6	18.5
Atazanavir	0.48	0.24

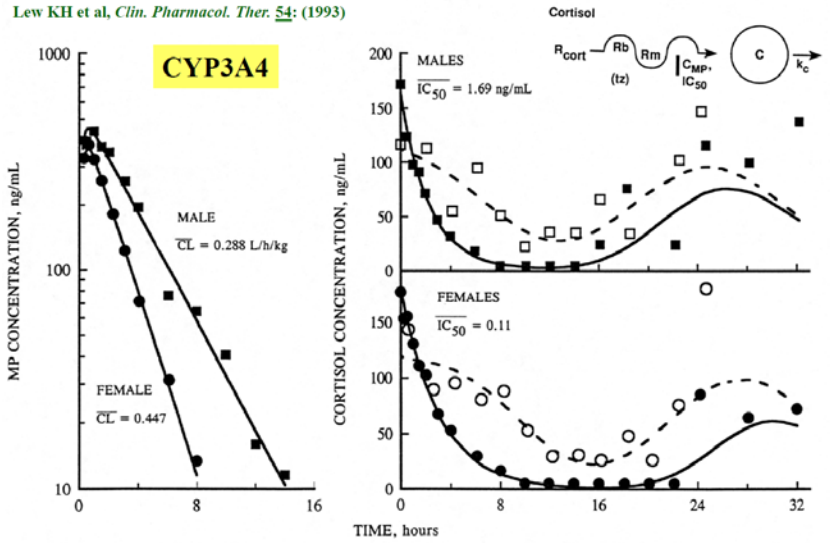
'Women are more likely to develop toxic concentrations…."

CYP3A4, 2D6

Ofotokun et al, *Gender Med.* 4: 106 (2007).

Gender and Methylprednisolone PK/PD

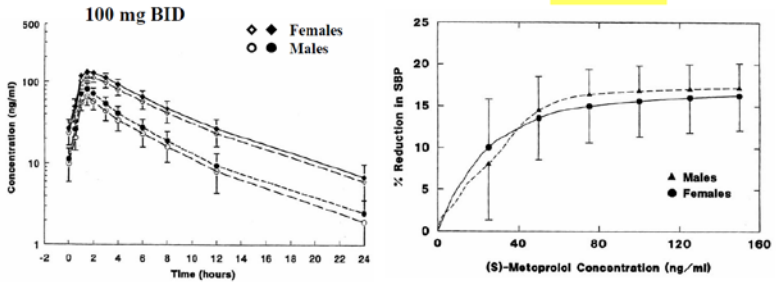
Lew KH et al, *Clin. Pharmacol. Ther.* 54: (1993)



Metoprolol PK/PD in Relation to Gender

A.B. Luzier et al, *Clin. Pharmacol. Ther.* 66: 594-601, 1999.

CYP2D6

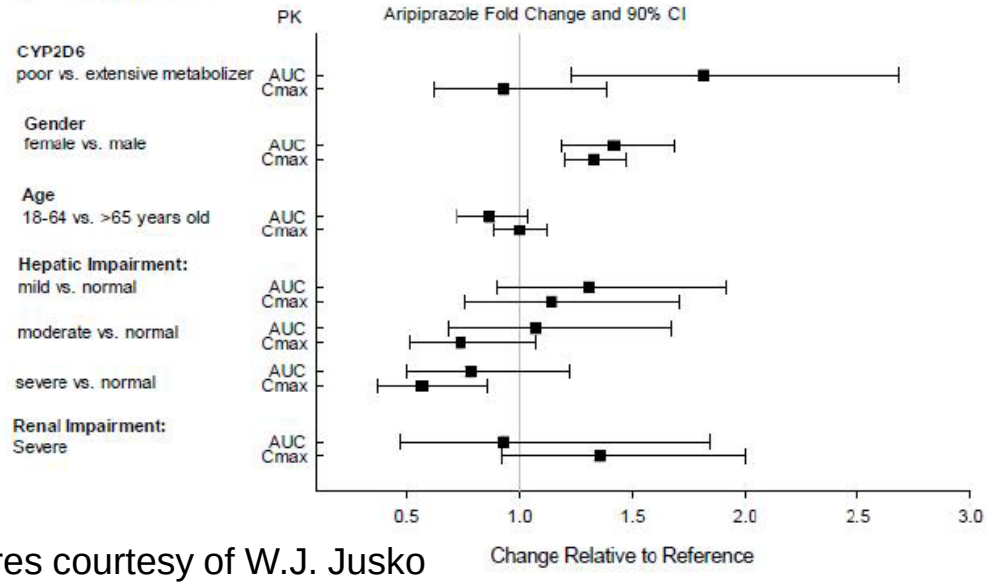


Clearances (L/hr/kg)

	Men	Women
(S)-met.	2.21	1.16
(R)-met.	3.40	1.44

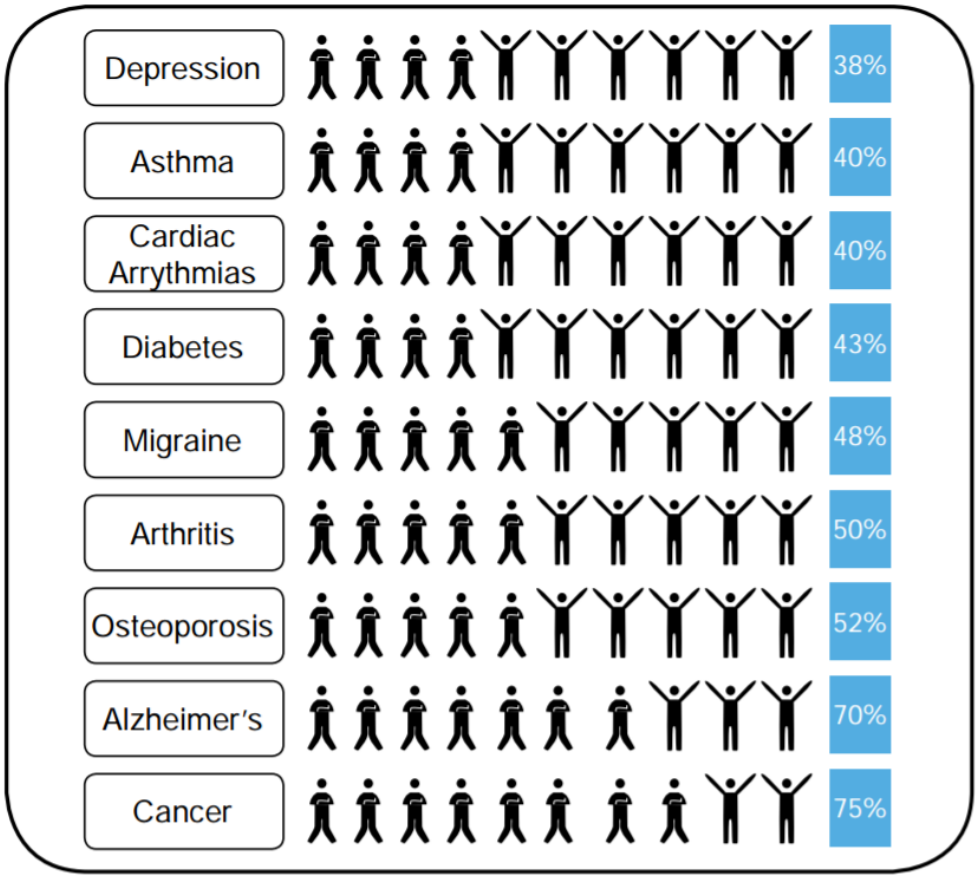
Pharmacodynamics : SBP

	Men	Women
E_{max}, %	18.0	17.8
EC_{50}, ng/ml	28.1	25.4



Figures courtesy of W.J. Jusko

Some things we are trying to figure out



Trends in Mol. Med. **7**(5)"201-204 (2001)

Personalized medicine

The NEW ENGLAND JOURNAL of MEDICINE

"*steering the right patients to the right drug at the right dose at the right time*"

Perspective

JULY 22, 2010

The Path to Personalized Medicine

Margaret A. Hamburg, M.D., and Francis S. Collins, M.D., Ph.D.

Personalized medicine

"medical decisions, practices, interventions and/or products being tailored to the individual patient based on their predicted response or risk of disease"


FORUM
Academy of Medical Sciences

Stratified, personalised or P4 medicine: a new direction for placing the patient at the centre of healthcare and health education (May 2015)

Summary of a joint FORUM meeting held on 12 May 2015.

Supported by the Academy of Medical Sciences, the University of Southampton, Science Europe and the Medical Research Council.

MRC Medical Research Council

SCIENCE EUROPE

UNIVERSITY OF Southampton

Personalized medicine

The use of genomic information – in addition to family history, lifestyle, and environmental factors – to customize health management. By combining genomic and clinical information, more accurate predictions can be made about a person's susceptibility of developing disease, the course of disease, and response to treatment.

The origins of *personalized medicine*

"Kimono, kimono, kimono? Ha!
Of course! Kimono is come from the
Greek word *himona*, is mean 'winter.'
So, what do you wear in the wintertime
to stay warm? A robe.
You see: robe, kimono. There you go!"

"It is more important to know what sort of person has a disease, than to know what sort of disease a person has"

Hippocrates extended Alcmaeon's doctrine, along with Epedocles's concept of the four elements, to define four basic humors: sanguis/blood (air), phlegm (water), choler (fire), and melancholia (earth). Choler and melancholia were sometimes referred to as yellow and black bile, respectively. Disease was considered to be the result of an imbalance (*dyscrasia*) between these humors, and it was the role of the physician and patient to try to reestablish a proper equilibrium (*eucrasia*). A word we use today, "complexion," was derived from the practice of complexing the four humors to define the unique characteristics of each individual and their state of health, a practice we might now refer to as *phenotyping*. We can still classify people today as being "good-humored" or "ill-humored," as a result of the primary role of the humors in early medical practice.

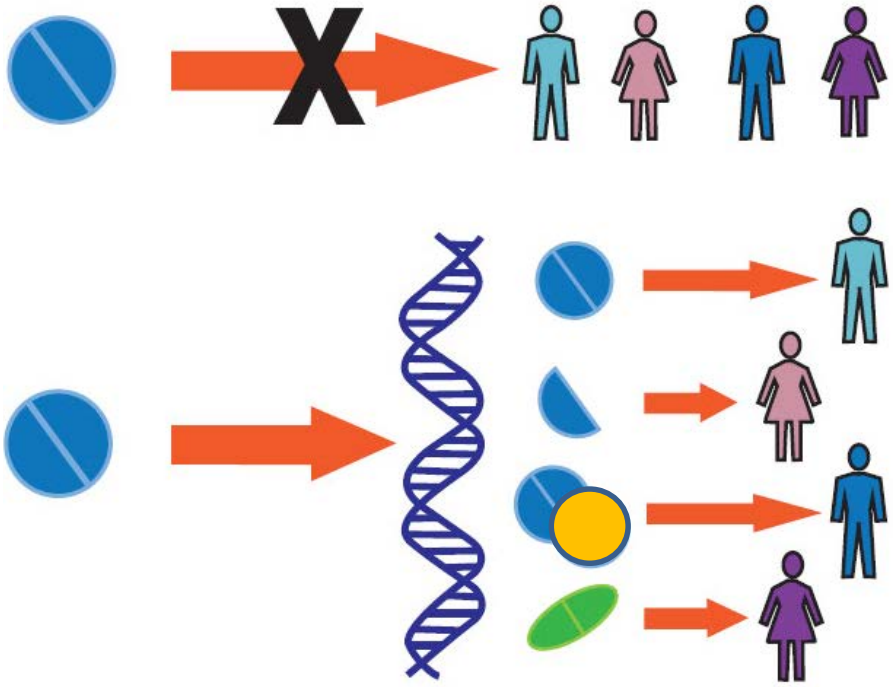
Early examples of personalized medicine

1907: Reuben Ottenberg reports the first known blood compatibility test for transfusion using blood typing techniques and cross-matching between donors and patients to prevent hemolytic transfusion reactions.

1956: The genetic basis for the selective toxicity of fava beans ("favism") and the antimalarial drug primaquine is discovered to be a deficiency in the metabolic enzyme, glucose-6-phosphate dehydrogenase (G6PD).

1977: Cytochrome P450 2D6, a polymorphic metabolizing enzyme, is identified as the culprit for causing some patients to experience an "overdose" or exaggeration of the duration and intensity of the effects of debrisoquine, a drug used for treating hypertension.

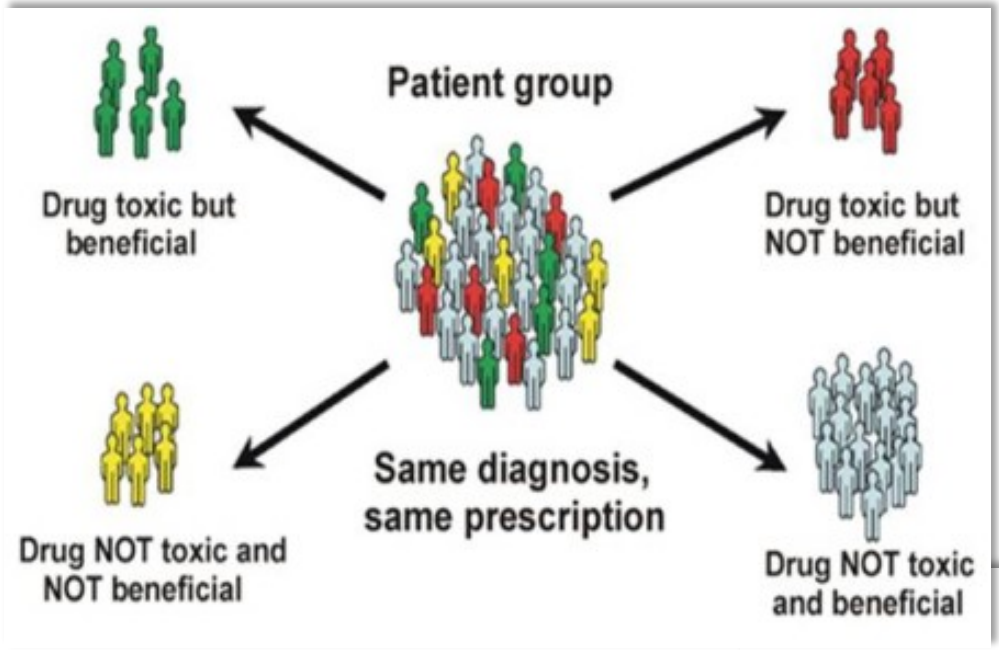
The basic tenet of gene-centric personalized medicine

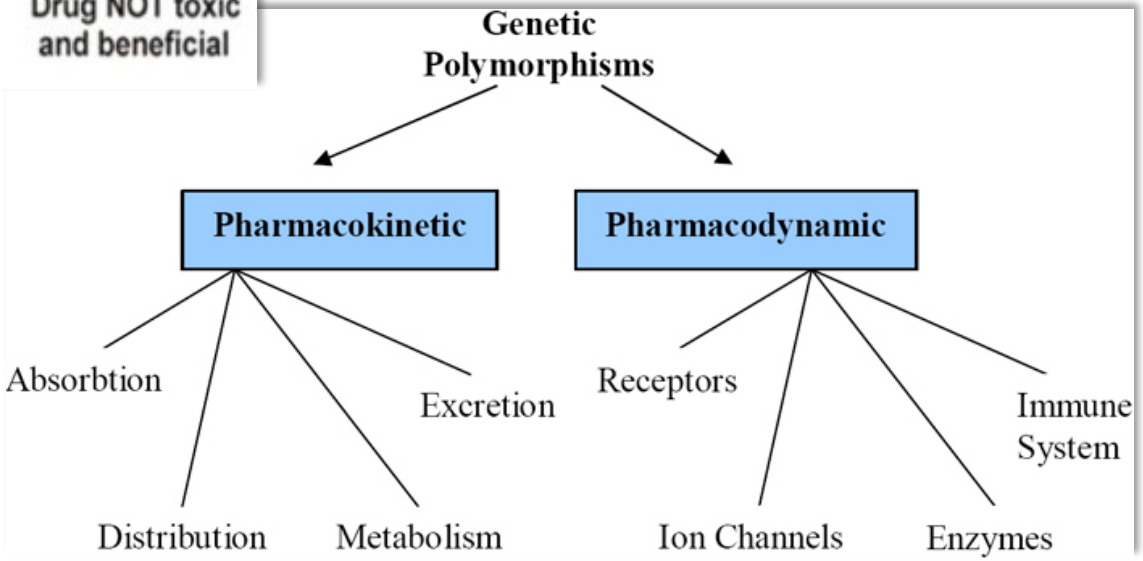


"Using tumor profiling to better understand how patients' tumors become resistant to cancer therapy

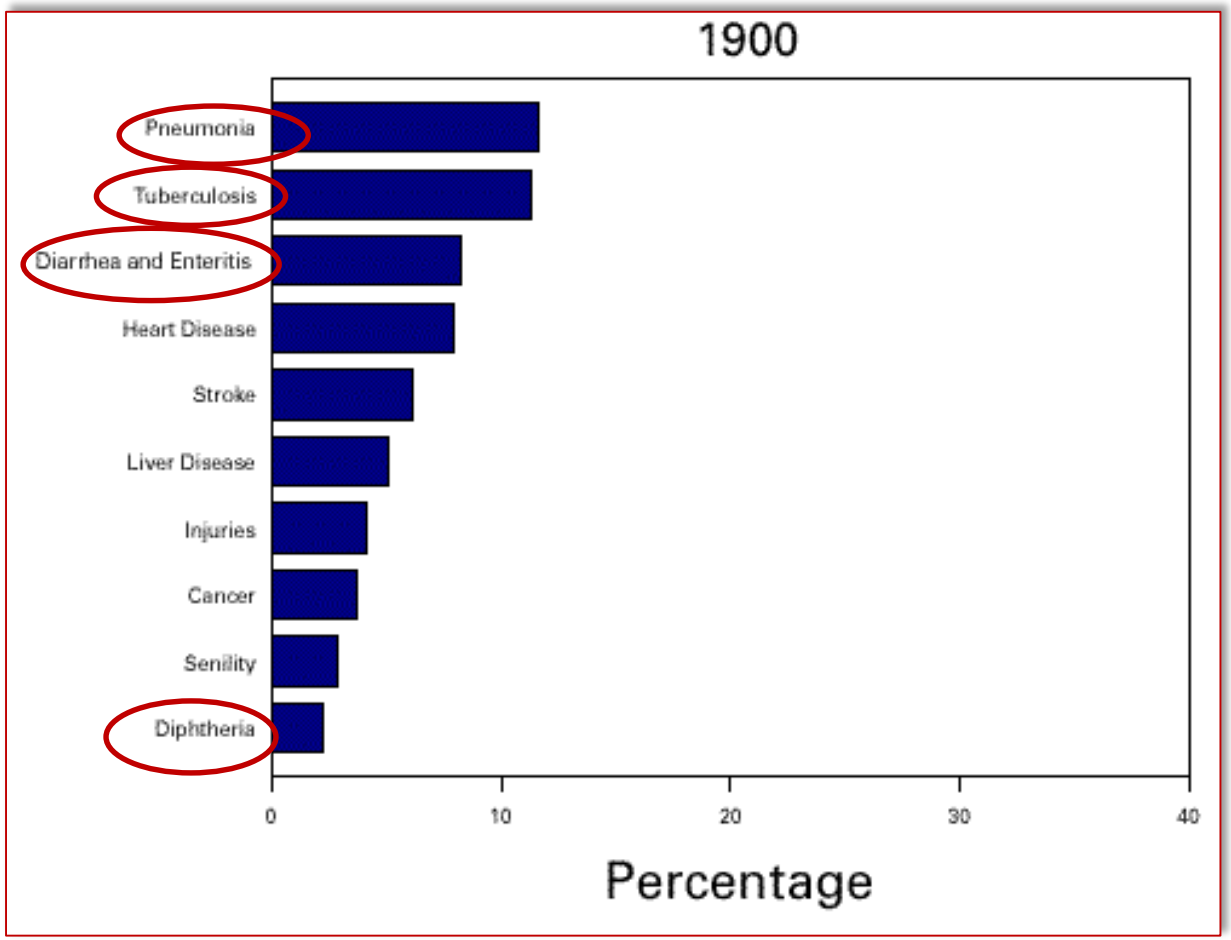
Establishing a repository of laboratory models derived from patient tumor samples that will enable researchers to more thoroughly investigate drug resistance"

PGx and personalized medicine



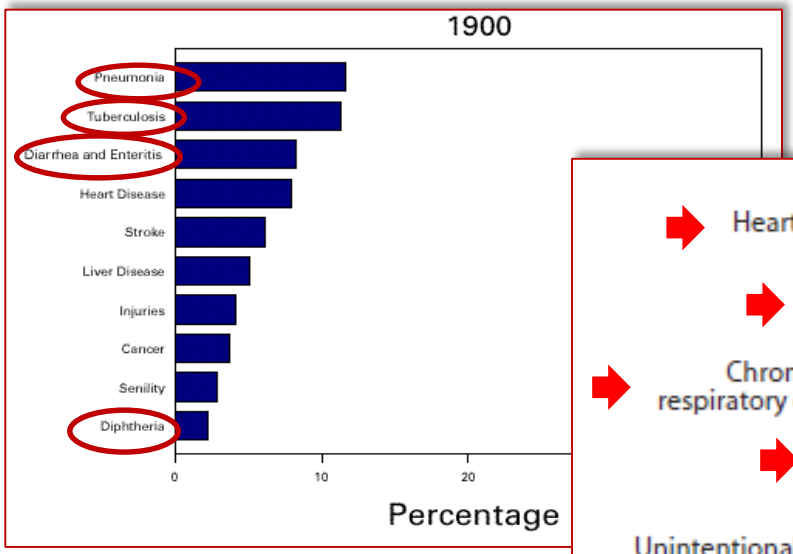


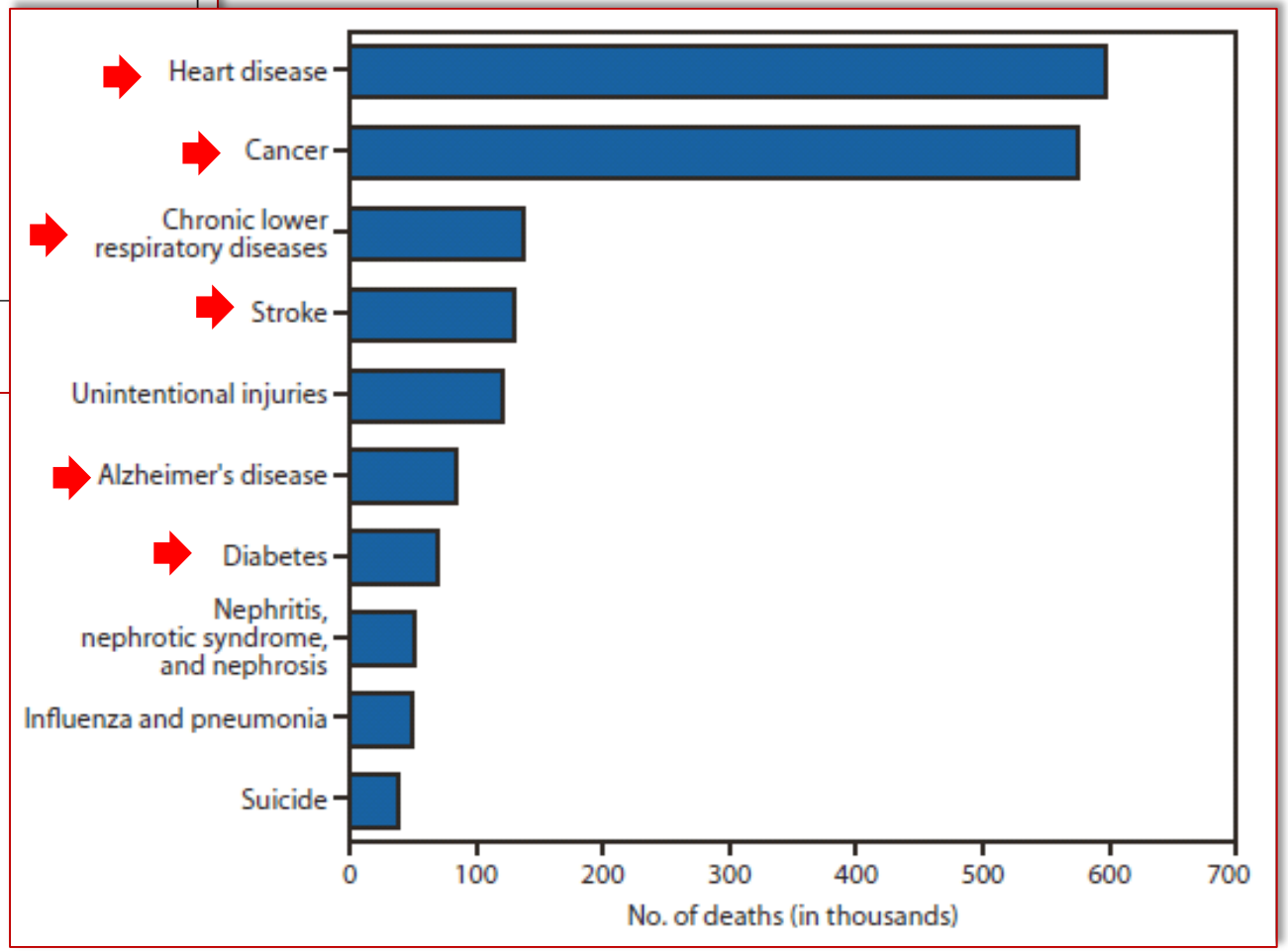
Leading causes of death in the USA in the early 1900's



https://www.cdc.gov/mmwr/preview/mmwrhtml/mm4829a1.htm

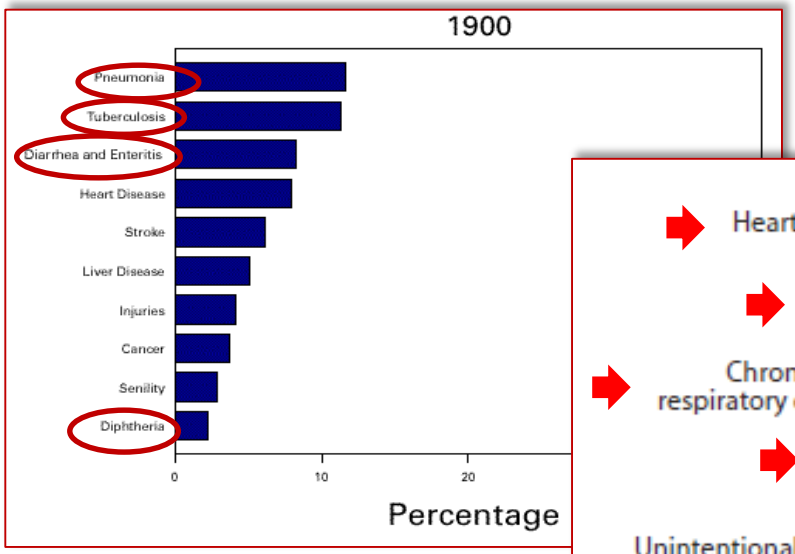
Leading causes of death in the USA in 2010

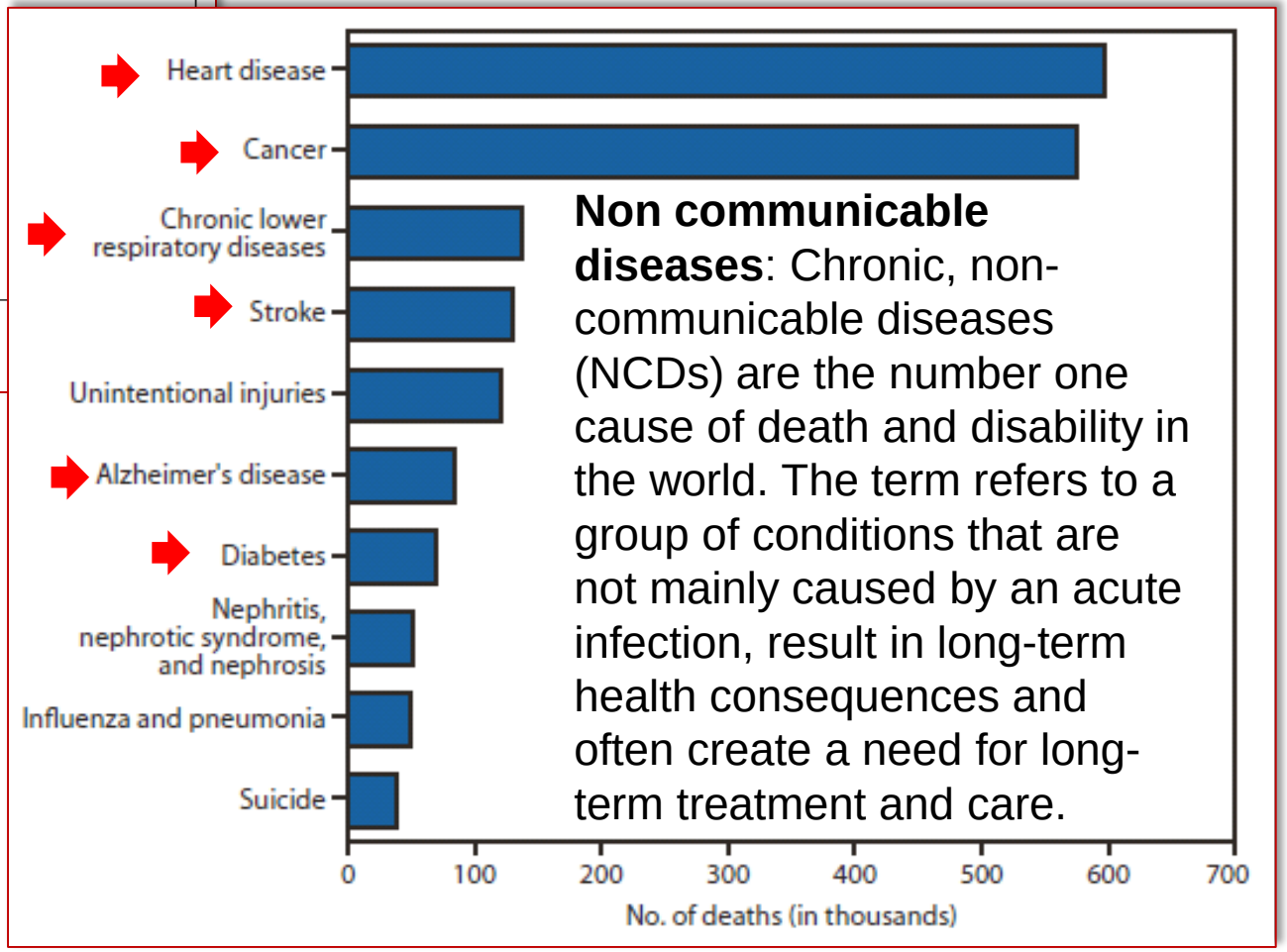




https://www.cdc.gov/mmwr/preview/mmwrhtml/mm6208a8.htm

Leading causes of death in the USA in 2010

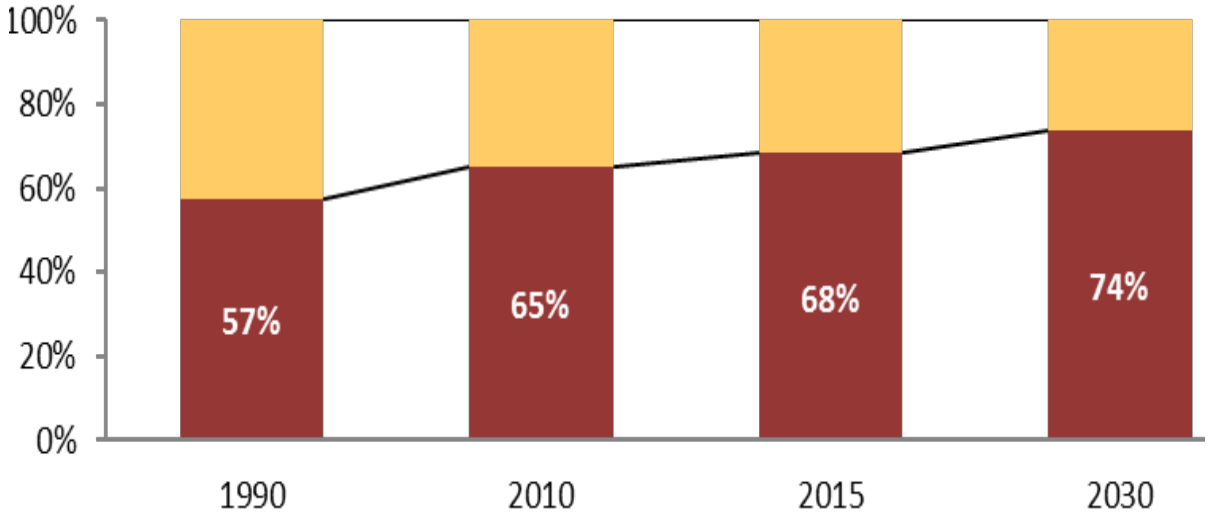


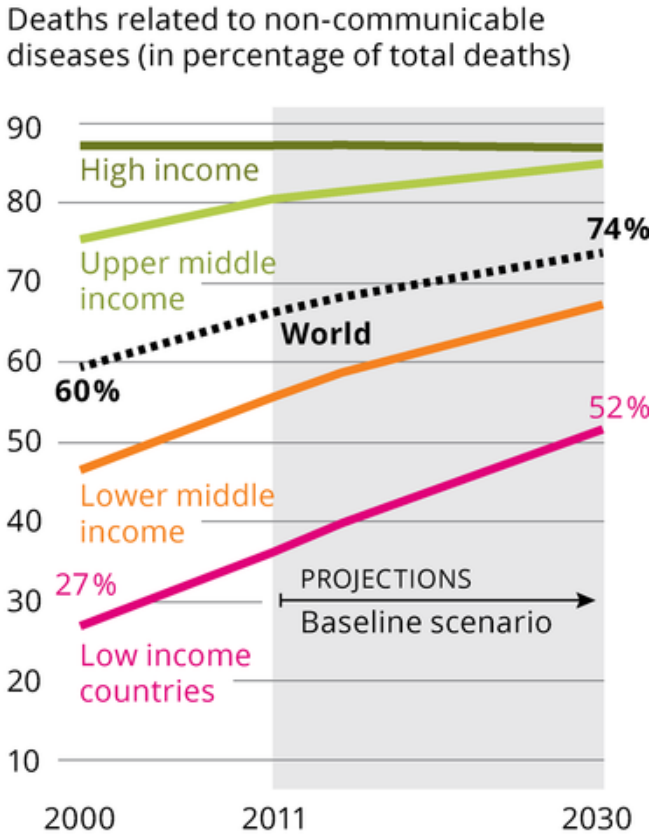


Non communicable diseases: Chronic, non-communicable diseases (NCDs) are the number one cause of death and disability in the world. The term refers to a group of conditions that are not mainly caused by an acute infection, result in long-term health consequences and often create a need for long-term treatment and care.

https://www.cdc.gov/mmwr/preview/mmwrhtml/mm6208a8.htm

The rise of *non-communicable diseases*: Mortality



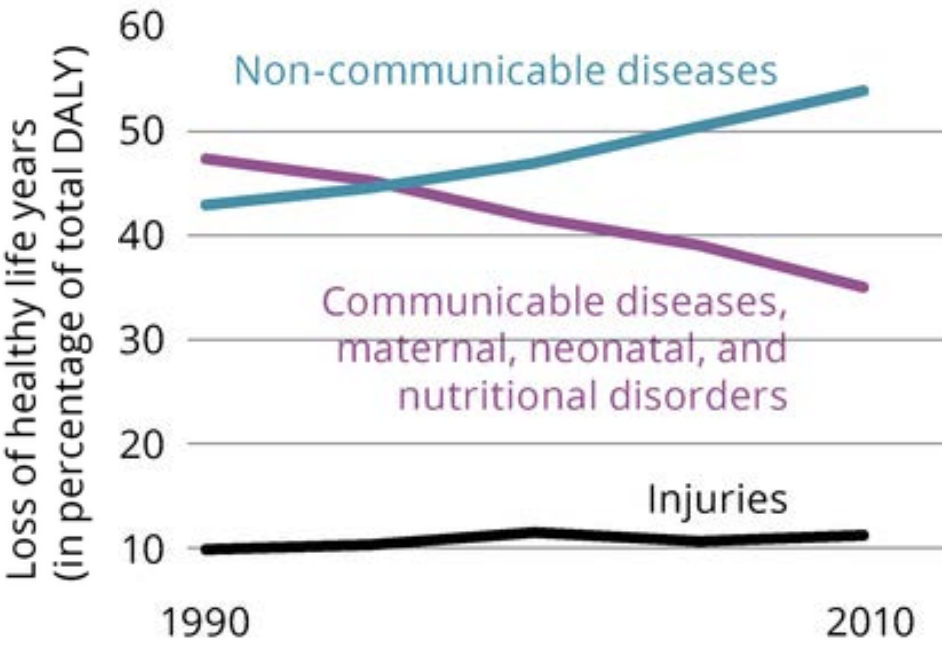


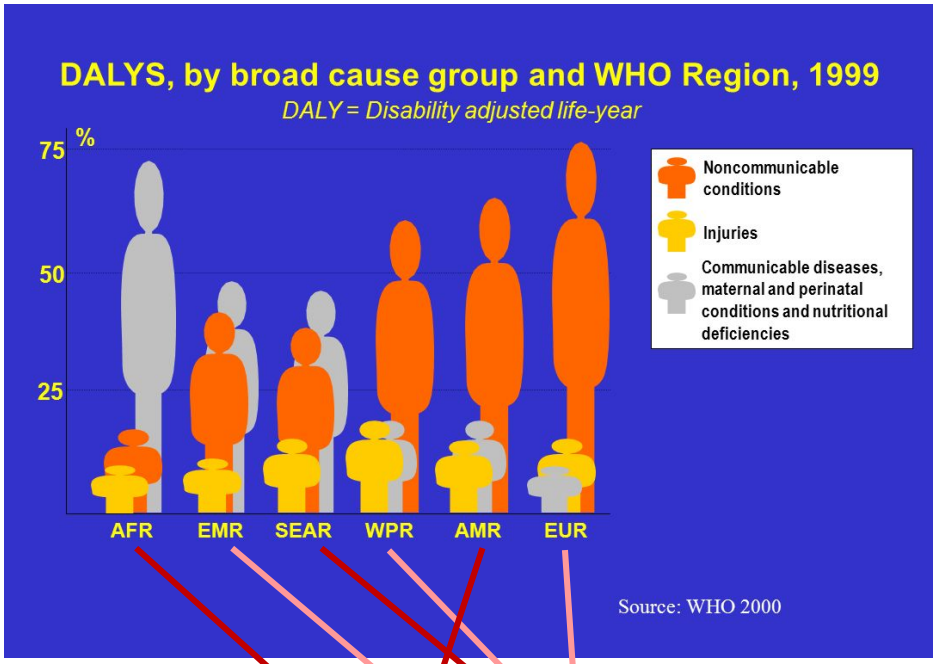
Source: Lozano et al. 2012; WHO projections of mortality and causes of death (http://www.who.int/healthinfo/global_burden_disease/projections/en/)

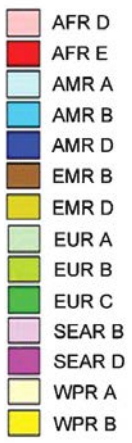
http://www.eea.europa.eu/data-and-maps/figures/the-shift-in-global-disease

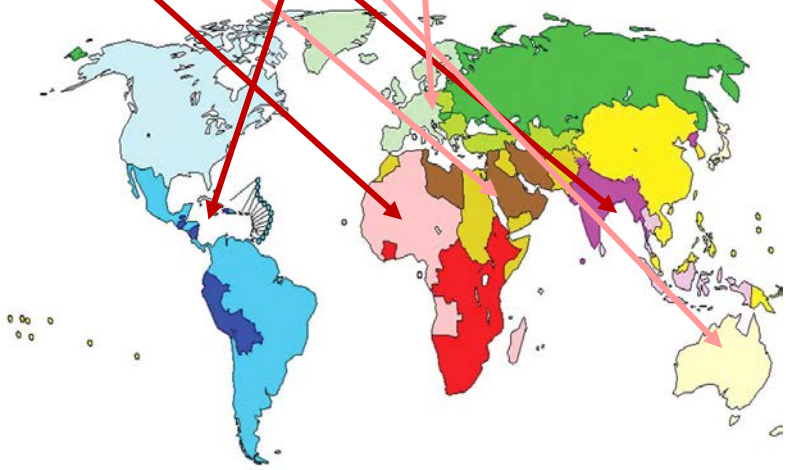
The rise of *non-communicable diseases*: DALY

Disability Adjusted Life Years (DALY) is defined by the WHO as “the sum of years of potential life lost due to premature mortality and the years of productive life lost due to disability”



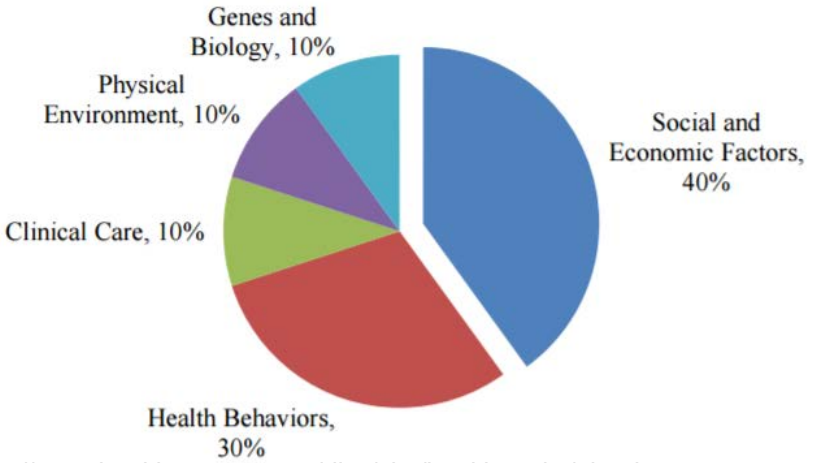




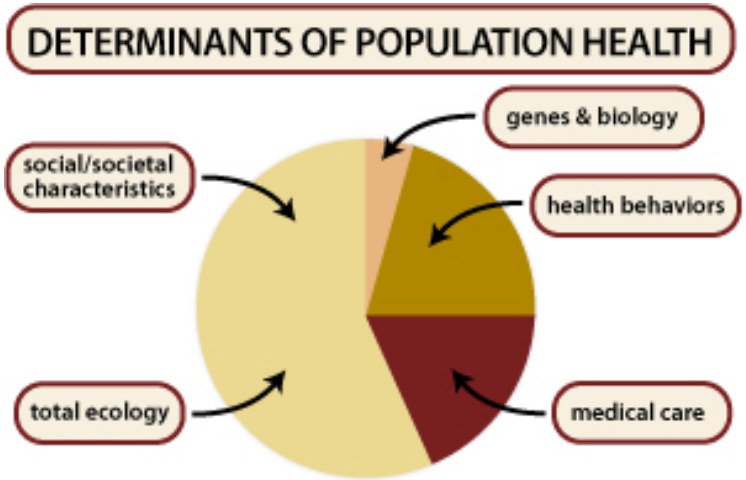


http://www.eea.europa.eu/data-and-maps/figures/the-shift-in-global-disease

NCD and the determinants of health in the 21st century



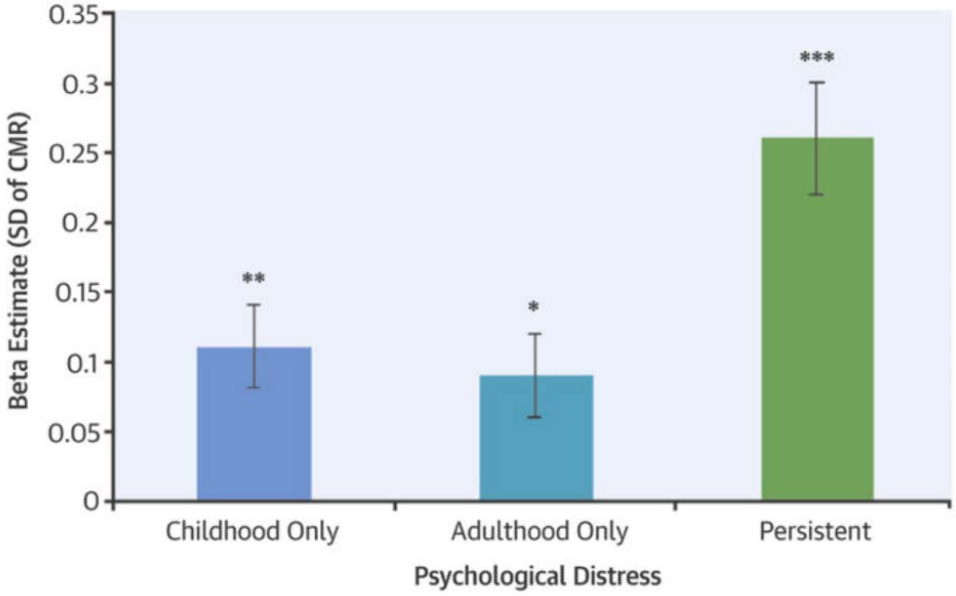
http://www.health.state.mn.us/divs/chs/healthequity/ahe_leg_report_020414.pd



Public Policy Frameworks for Improving Population Health

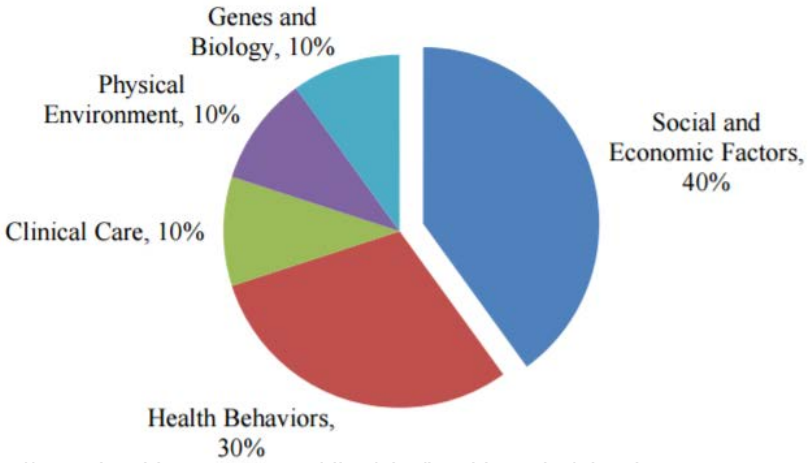
ALVIN R. TARLOV[a,b]
The Health Institute, New England Medical Center, Harvard School of Public Health, Tufts University School of Medicine, USA

Psychological distress at any point in the life course is associated with higher cardio-metabolic risk



JACC, ***66***:1577 (2015)

NCD and the determinants of health in the 21st century



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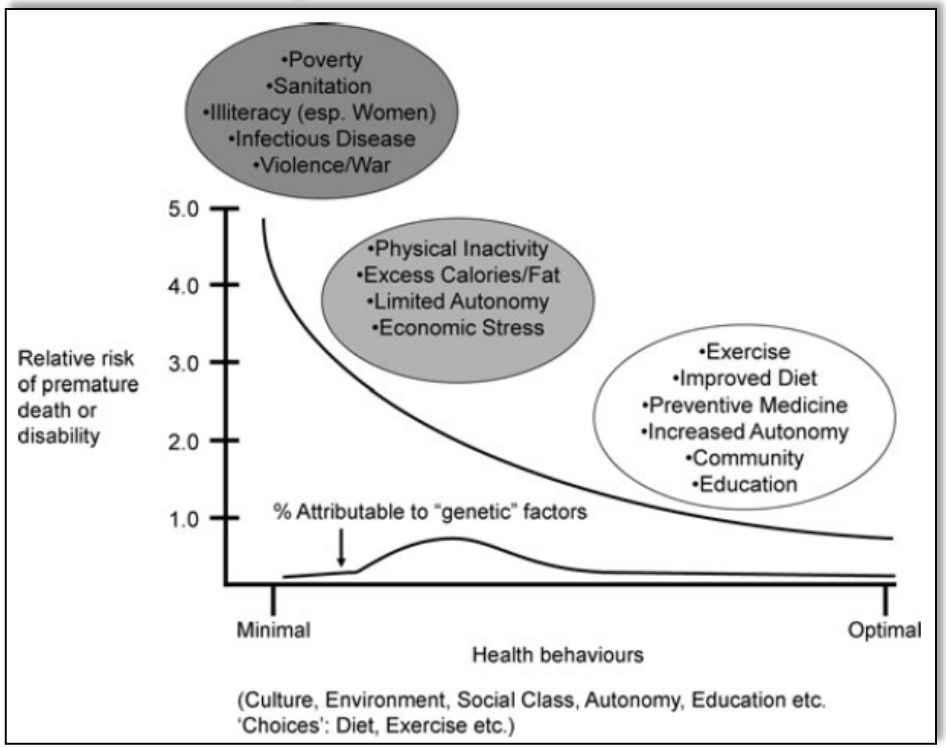

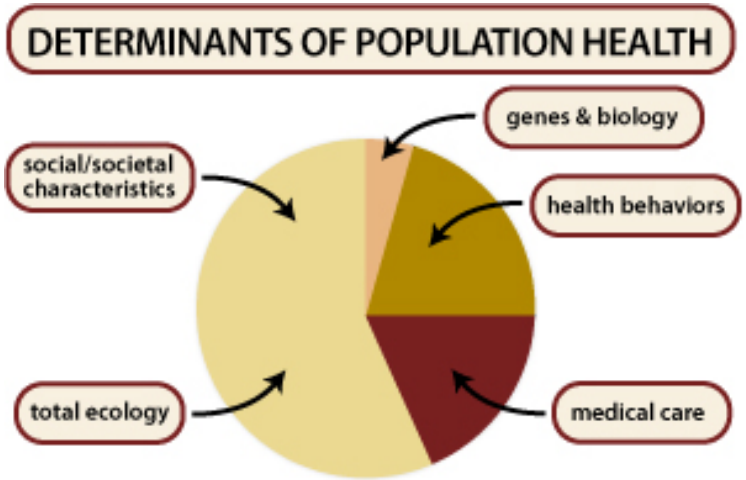

Public Policy Frameworks for Improving Population Health

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Ten questions about systems biology

Michael J. Joyner[1] and Bente K. Pedersen[2]

[1]*Department of Anesthesiology, Mayo Clinic, Rochester, MN, USA*
[2]*Centre of Inflammation and Metabolism (CIM), University of Copenhagen, Faculty of Health Sciences, Copenhagen, Denmark*

Personalized medicine: not just in your genes

289 cardiovascular pharmacogenomics studies

229 reported positive findings

220 unique SNP-drug associations

19 confirmed using strict criteria

0 recommended for use in clinical practice

"the notion that genetic information is uniquely important in determining the risks and benefits of treatments—is clearly unwarranted and counterproductive to the broadly shared goal of tailoring care to individuals"


BMJ

BMJ 2012;344:e2161 doi: 10.1136/bmj.e2161 (Published 3 April 2012) Page 1 of 5

Personalised medicine: not just in our genes

Despite the identification of numerous gene-drug associations, few have been incorporated into clinical practice or guidelines. **Georgios D Kitsios** and **David M Kent** argue that if personalised medicine is to become a reality we have to look beyond our genes

Georgios D Kitsios *researcher*[1 2], David M Kent *director*[3 1]

Personalized medicine: not just in your genes

"the contribution of genetic discoveries to the clinical management of diabetes and obesity remains limited to the small proportion of cases with monogenic forms of disease"

REVIEW ARTICLE

GENOMIC MEDICINE

W. Gregory Feero, M.D., Ph.D., Editor, Alan E. Guttmacher, M.D., Editor

Genomics, Type 2 Diabetes, and Obesity

Mark I. McCarthy, M.D.

N Engl J Med 2010; 363:2339-2350 | December 9, 2010 | DOI: 10.1056/NEJMra0906948

What is special about non-communicable diseases ?

NCD (CVD, Diabetes, Chronic Respiratory Disease, Cancer) are chronic conditions heavily influenced by urbanization (behavioral, environmental, socio-economic factors)

There is no cure for any of these diseases, only symptom mitigation, because it is not clear what the underlying cause it (I think …)

"Indeed, finding a cure for established RA is possibly no more likely than finding a cure for hypertension, where control of organ damage is the only realistic goal of therapy"


VOLUME 4 SUPPLEMENT 3
The Scientific Basis of Rheumatology

REVIEW | OPEN ACCESS

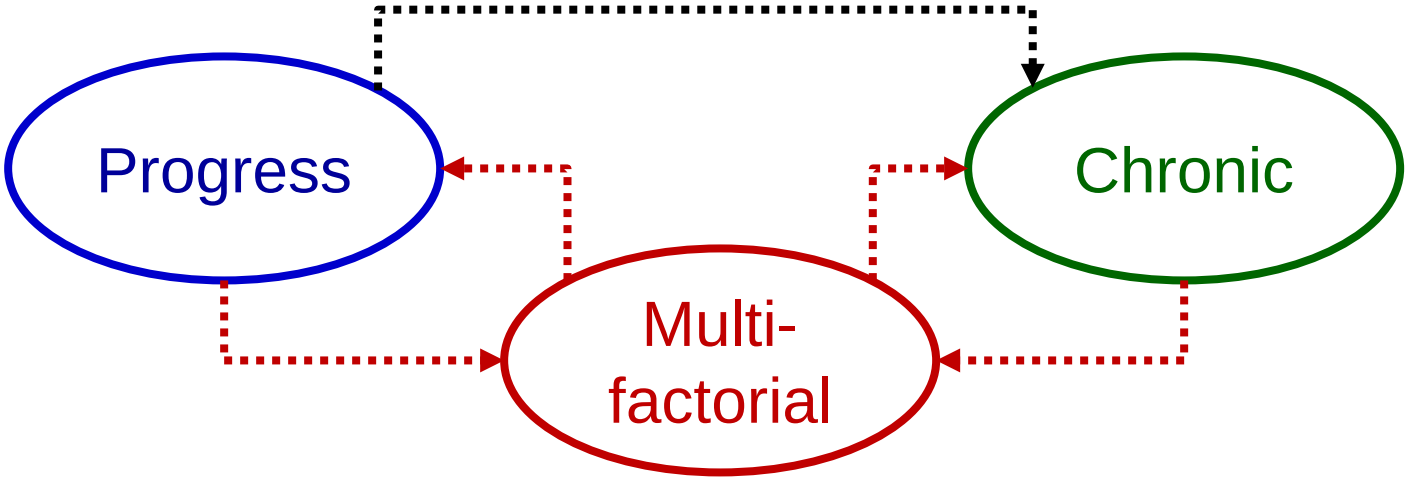
Why do we not have a cure for rheumatoid arthritis?

Hani D El-Gabalawy and Peter E Lipsky

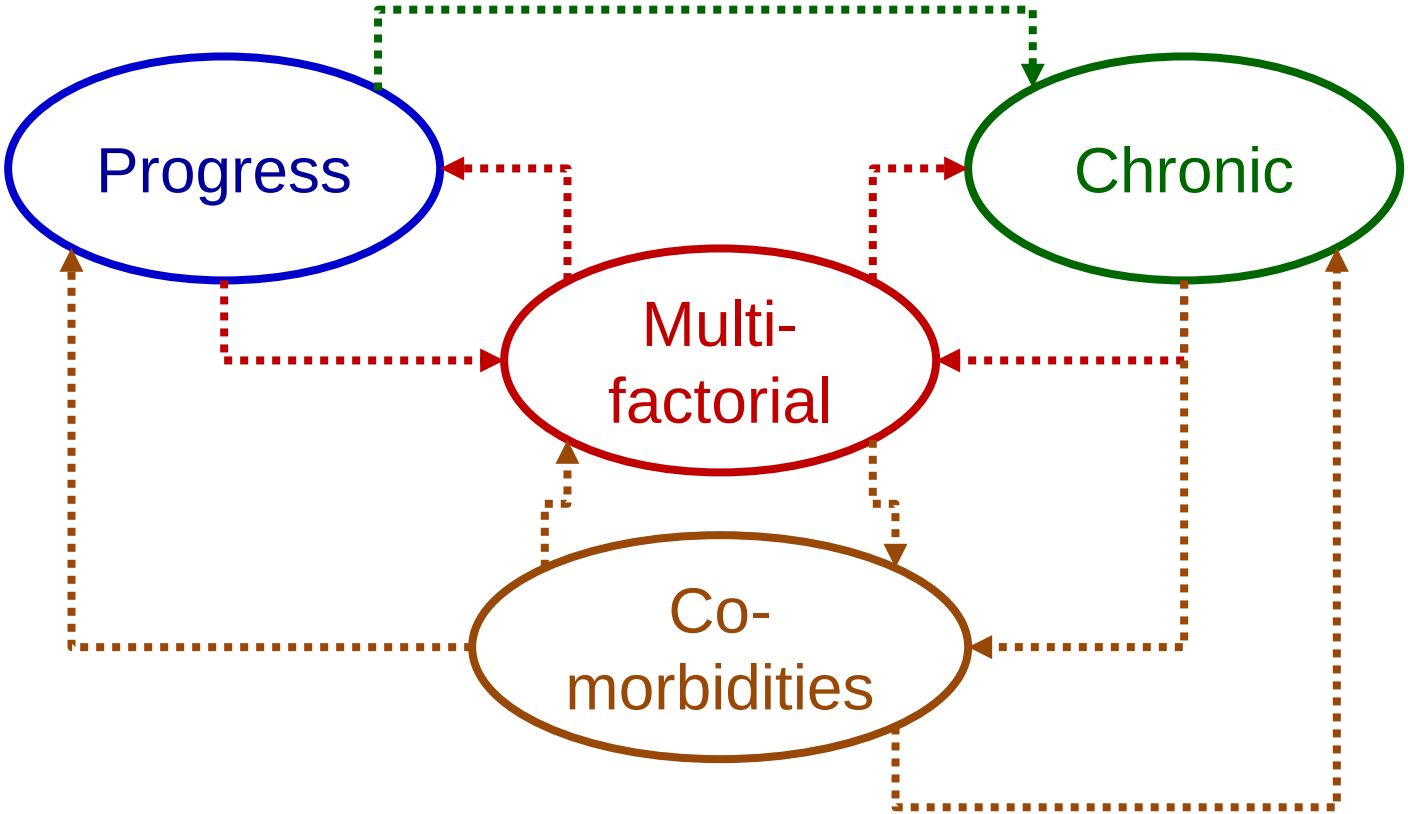
The emergent complexities of NCD

The emergent complexities of NCD

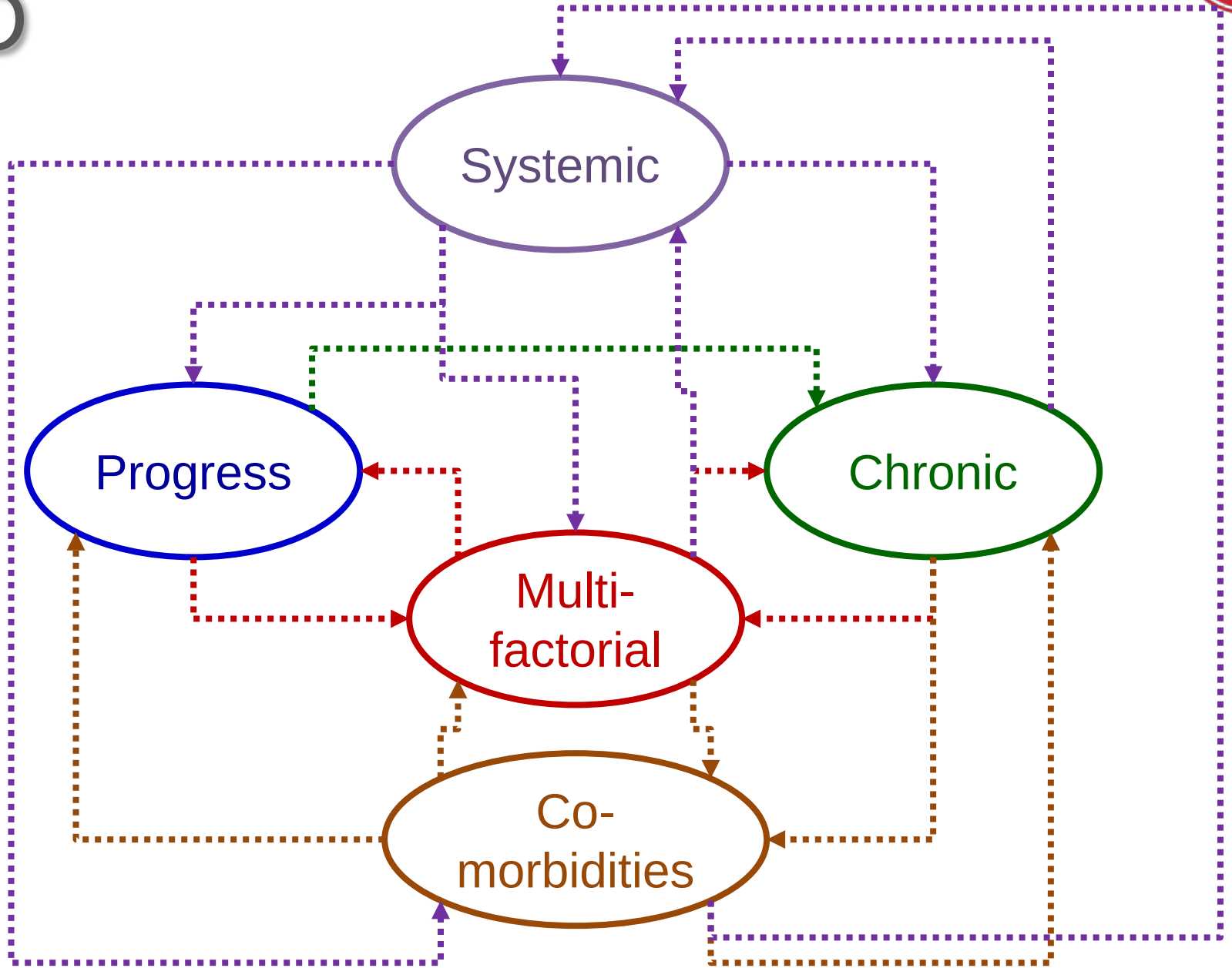
The emergent complexities of NCD



The emergent complexities of NCD



The emergent complexities of NCD



A systems view …

Environmental enrichment (nest making) and oxytocin (brain neuromodulator hormone) comparably promote burn wound healing in isolation reared rats (*PLosONE,* **4**:e5523, 2009)

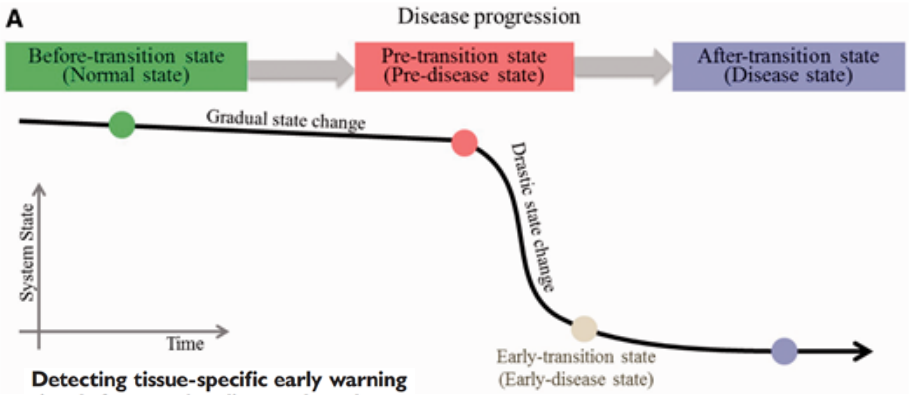
Desynchronization produced by meal timing during the rest period slowed down tumor progression (*Life Sci.,* **75**:1181, 2004). Temporally scheduled feeding during the rest period reverses some of the liver-specific metabolic abnormalities in a mouse model of *Huntington's* disease (*J. Neurosci.*, **303**:10199, 2010); HF diet and tRF (*Cell Met.,* **15**:848, 2012)

Biofeedback modulation of HRV modulates autonomic effects in inflammation (*Appl. Psych. Biof.*, **35**:303, 2010); Yoga as complementary pulmonary tuberculosis therapy (*Resp.* **9**:91, 2004) – Yoga drives ANS-related effects in epilepsy, depression, PTSD (*Med. Hyp.*, **78**: 571, 2012)

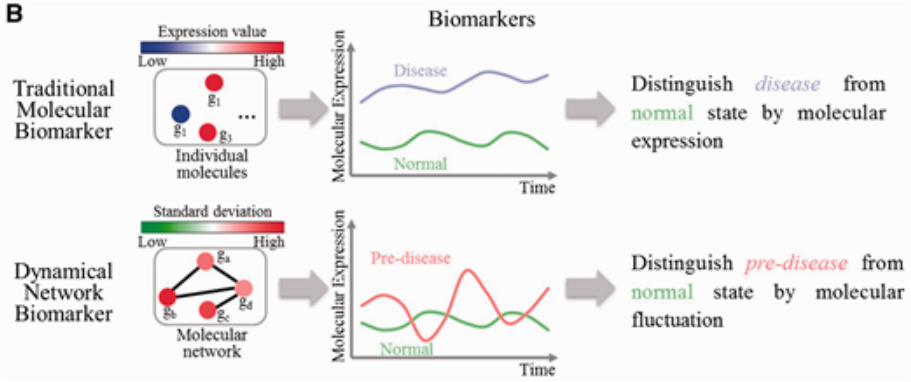
Expectation of therapeutic benefit (placebo) activates brain regions evoking release of dopamine, brain derived neurotropic and growth factors (*Science*, **293**:1164, 2001) – Genomic studies confirmed positive placebo with baseline u/s – d/s dopamine pathway interactions (*Trends Mol. Med.,* in press).

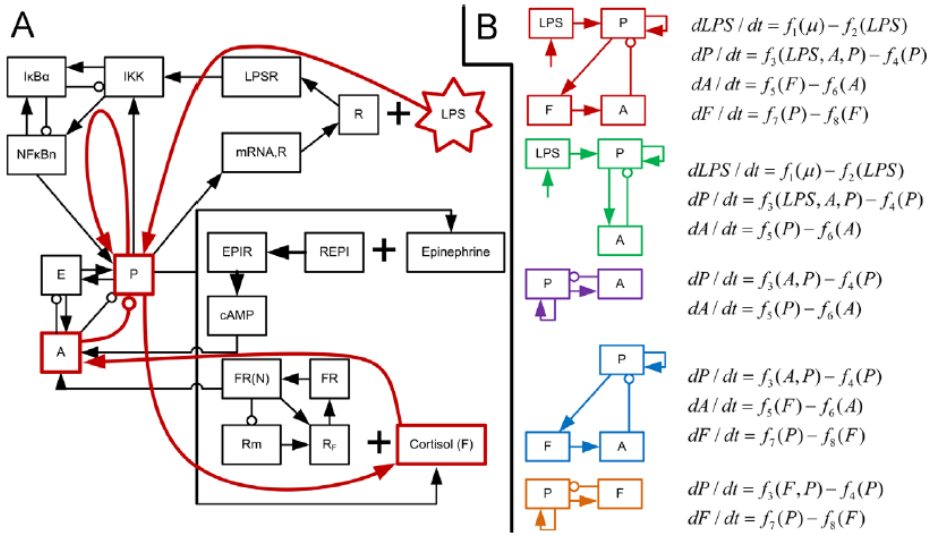
Expectation of fear HR, inflammation & ANS (*PNAS*, **112**:1248, 2015)

Chronic disease & critical transitions: A systems dynamic perspective



Detecting tissue-specific early warning signals for complex diseases based on dynamical network biomarkers: study of type 2 diabetes by cross-tissue analysis





$$dLPS/dt = f_1(\mu) - f_2(LPS)$$
$$dP/dt = f_3(LPS, A, P) - f_4(P)$$
$$dA/dt = f_5(F) - f_6(A)$$
$$dF/dt = f_7(P) - f_8(F)$$

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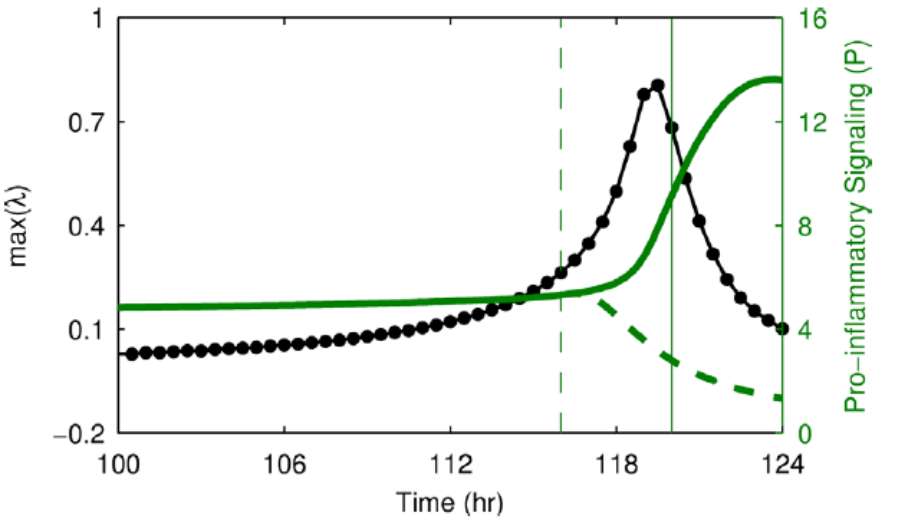
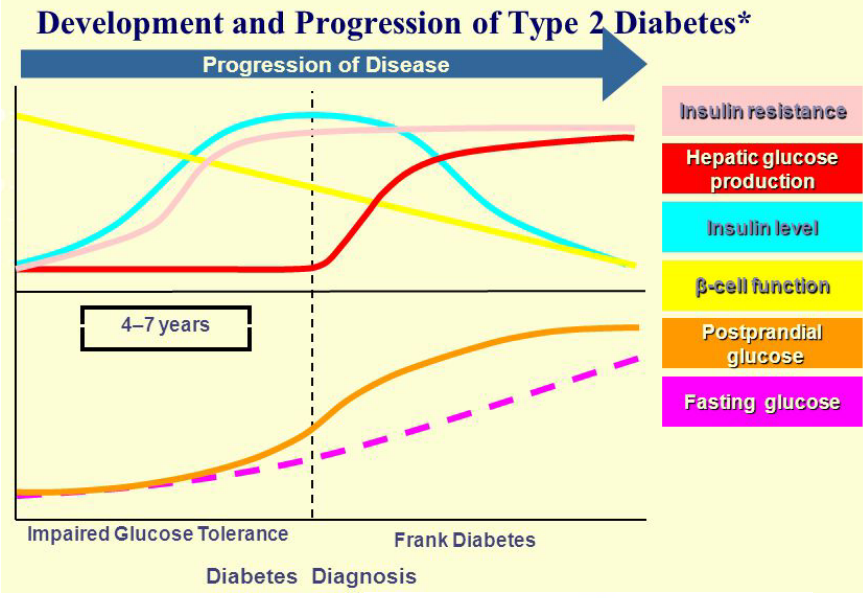
$$dF/dt = f_7(P) - f_8(F)$$



Predicting critical transitions in a model of systemic inflammation

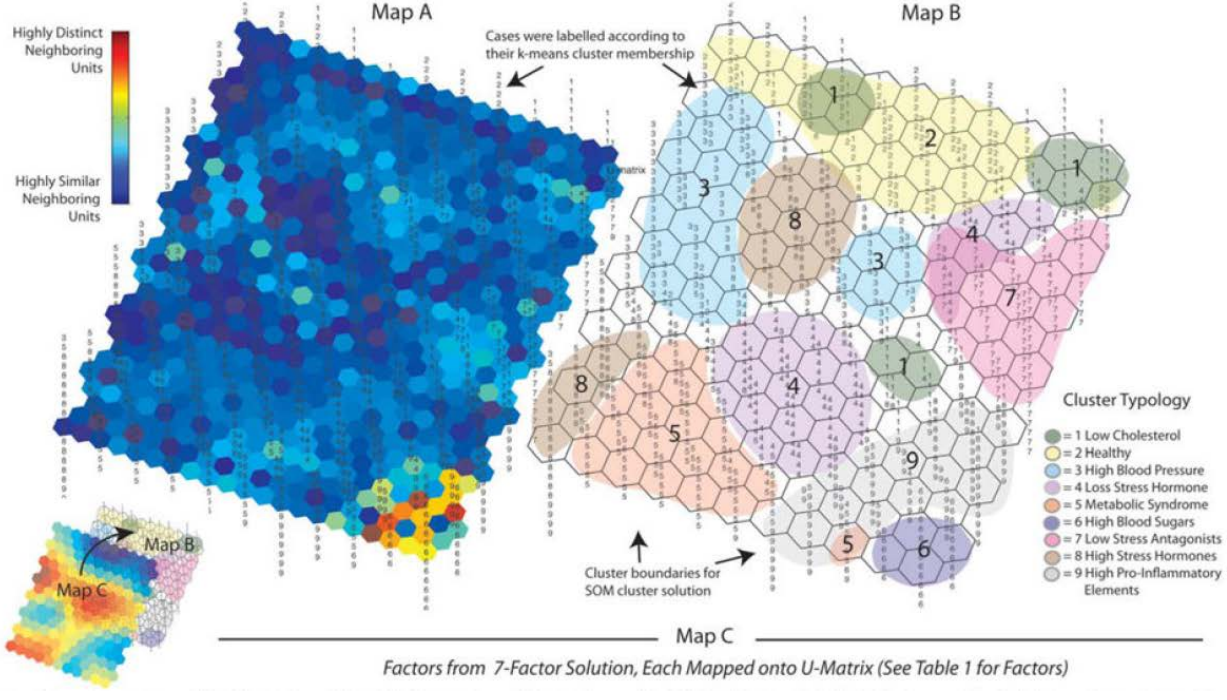
Jeremy D. Scheff[a], Steve E. Calvano[b], Ioannis P. Androulakis[a,b,c,*]

Disease progression and allostatic load



Complexity. 2016 ; 21(Suppl 1): 291–306. doi:10.1002/cplx.21743.

Allostatic Load as a Complex Clinical Construct: A Case-Based Computational Modeling Approach



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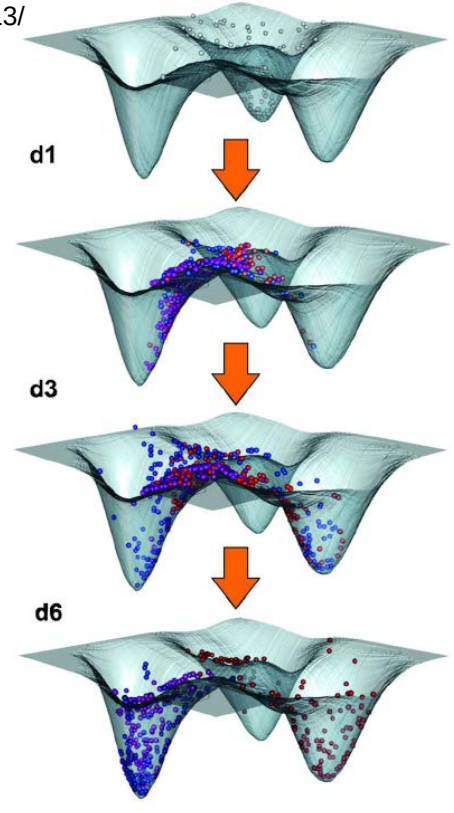
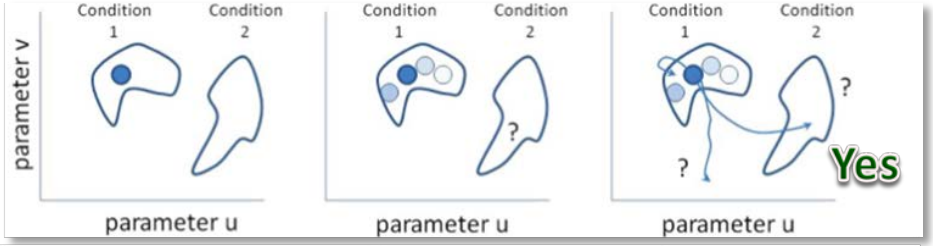
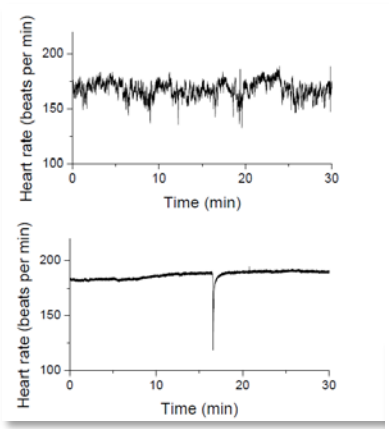


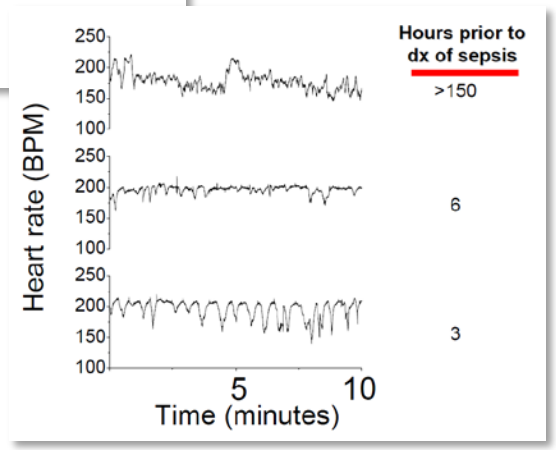
Can personalized medicine help us better describe the state of the patient ?

Critical transitions in clinical practice



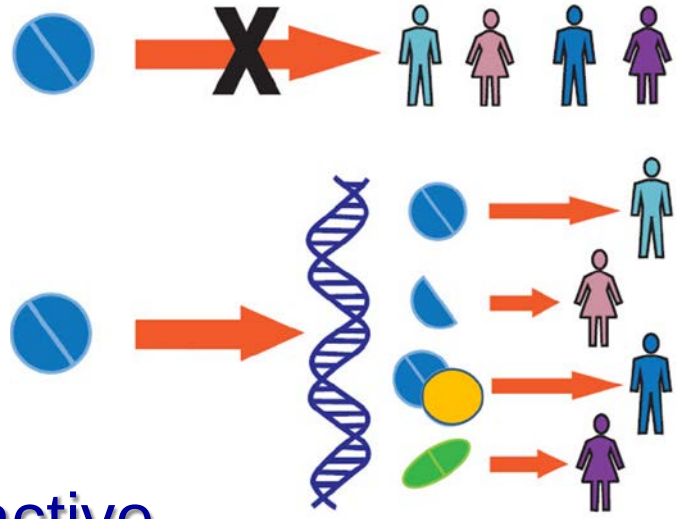
Buchman, *Crit. Care*, 2010





The ANS acts as a first integrator of the information describing the state of the host and generates an integrated signal which is then analyzed computationally. Changes in the dynamics of the integrated signal precede changes in individual biomarkers

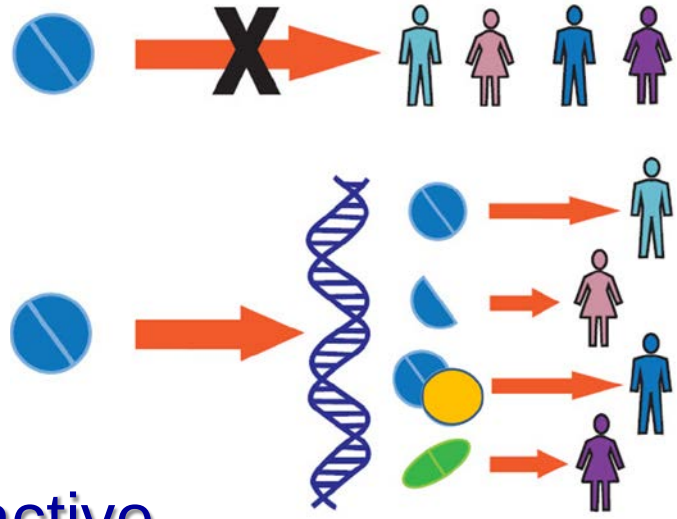
The faces of personalized medicine



Reactive

http://medicine.iupui.edu/IIPM

The faces of personalized medicine



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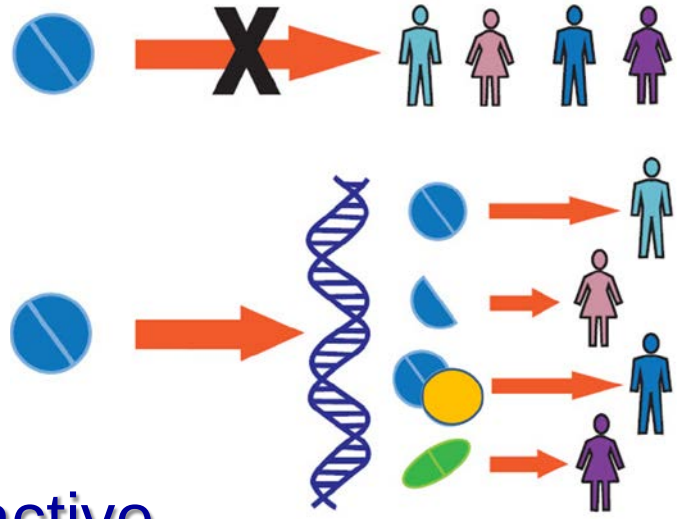
Predictively Reactive

The faces of personalized medicine



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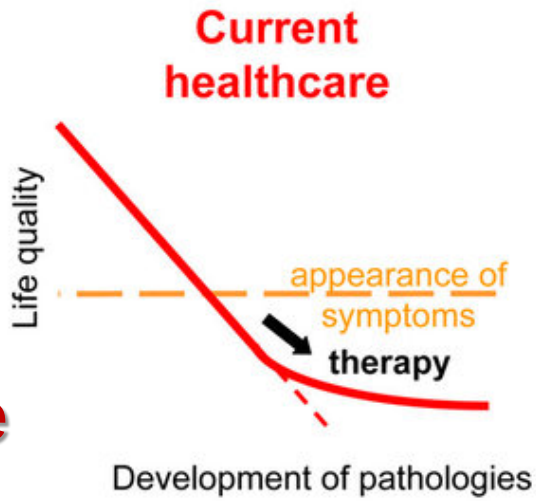
Predictively Reactive

Predictive



http://www.esa.int/spaceinimages/Images/2010/07/Advocating_predictive_medicine

Can personalized medicine transition from disease-centric to patient-centric ?

Should it reflect only genetics or also the evolving dynamics of the patient ?

If the answer is yes, then how do we achieve this and what complications (technical, ethical, societal, economic) do we foresee ?

P4 Medicine: *Predictive, Preventive, Personalized, Participatory*

Clinical OMICs INNOVATOR

Promoting Wellness & Demystifying Disease:

The 100K Project

Leroy Hood, M.D., Ph.D., and Nathan D. Price, Ph.D.

We believe that a longitudinal, Framingham-like study of 100,000 well individuals (hereafter termed the 100K project) and their dynamical data clouds could transform medicine by

1) providing scientifically validated metrics for wellness,

2) allowing one to study the earliest origins of disease in an individual and to allow one to follow the entire progression of a disease from its beginning to end.

This proposal would allow us to study the initiation and progression of all common diseases and, from that, learning how to predict and prevent these diseases would revolutionize healthcare.

Complexity, Disease, and Systems Medicine

Contemporary medicine is challenged by the incredible complexity of physiology and disease. Each individual has unique genetic and environmental contexts. Clearly the traditional reductionist approaches to disease are insufficient to effectively deconvolute this complexity. Over the last 10 years systems approaches have increasingly been employed, leading to a new discipline designated systems medicine, which has two striking features.

First, each patient will be surrounded by a virtual cloud of billions of data points, and we will have the analytical tools to reduce this enormous dimensionality to simple hypotheses of how to optimize wellness and minimize disease for each individual. Second, the data can be integrated and modeled to determine the health and disease-associated states of the "network of networks" operating in each individual. These interconnected networks manage diverse types of biological information that operate at the chromosomal, molecular, cellular, organ and even individual levels.

In disease, these networks become perturbed and this alters the information they manage and the functions they carry out. Delineating this altered and disease-perturbed information provides insights into disease mechanisms, diagnostic markers, and drug target candidates.

Systems medicine has reached a tipping point and its emerging technologies and systems-driven strategies are already beginning to alter the practice of medical discovery and of healthcare. Many strategies are helping to drive this future, such as using the complete genome sequencing of families to more rapidly identify disease genes, studying disease dynamics in model organisms to provide fundamental insights into disease mechanisms, pioneering systems approaches to blood diagnostics to create powerful biomarker panels that can inform medical decisions, stratifying diseases and patients into distinct subgroups for more personalized treatments, and using computational analyses of disease-perturbed networks to identify new classes of drug target candidates.

Nathan D. Price, Ph.D. is associate director and Leroy Hood, M.D., Ph.D., is president of the Institute for Systems Biology.

P4 Medicine

The convergence of systems medicine, big data and its analytics, and patient-activated social networks has led to a medicine that is predictive, preventive, personalized and participatory—P4 medicine. It differs from traditional evidence-based medicine in six ways: 1) it is proactive; 2) it focuses on the individual patient, 3) it emphasizes wellness, 4) it generates the personalized data clouds that provide fundamental insights into each individual, 5) it notes that the traditional path of clinical trials is ineffective and wasteful, and it suggests that clinical trials start with a deep analysis of the individual and not populations of dissimilar individuals; and 6) it contends that patient-activated social networks will be a major driving force in the medicine of the future.

P4 medicine embodies two central concepts—quantifying wellness and demystifying disease. The question is how do we bring P4 medicine to current healthcare systems? We believe the answer to that is through large-scale, information-rich longitudinal studies such as we are launching via the P4 pilot 100K project.

The 100K Project

The idea is to take 100,000 well patients and then carry out detailed genomic, proteomic, epigenetic, metabolomics, and phenotypic measurements on them four or more times a year—examining blood, saliva, stool as well as other physiological and psychological parameters. After time, these individuals would separate into two classes—those who remained well (or enhanced their health) and those who transitioned into disease.

From the data of those individuals who remained well or improved their health we could extract metrics for wellness. We could study those individuals transitioning from wellness to disease at the earliest stages of this transition—deciphering early disease mechanisms and generating early diagnostic markers. In time, the insights gained offer the possibility of transitioning patients very early on from the disease trajectory back to a wellness trajectory, saving the healthcare system enormous dollars by greatly shortening the costly disease trajectory and, most importantly, greatly enhancing the individual's quality of life.

Assays and Analytics

The starting basis will be a whole genome sequence for each participant in order to have information about the building blocks of each individual's physiology. This will only need to be done once, but a host of other measures will provide details on the dynamic changes in health that occur over time by interaction with the environment. Thus, we will employ digital devices that continuously measure physiological parameters like heart rate, activity, sleep quality, blood pressure, and weight.

We will periodically measure the gut microbiome, clinical chemistries with a focus on nutrition, blood

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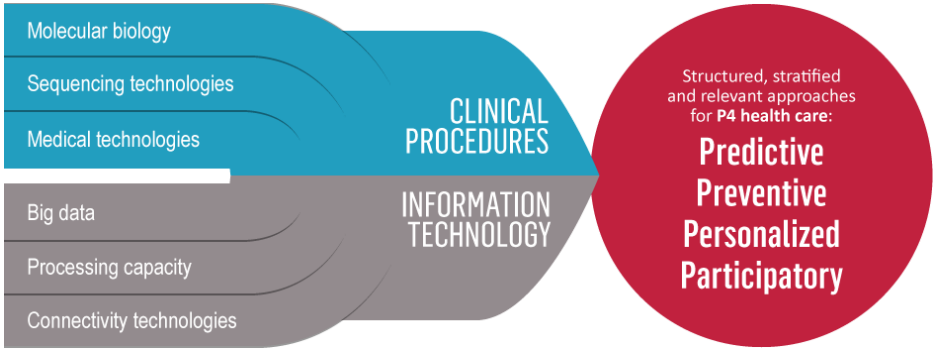
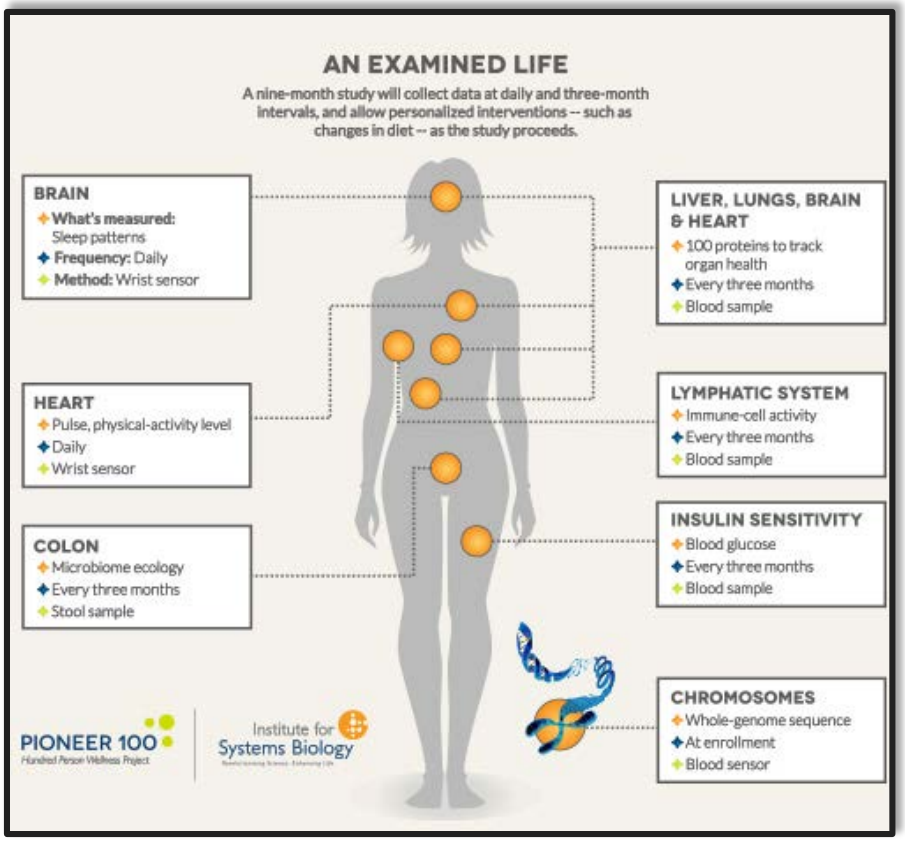
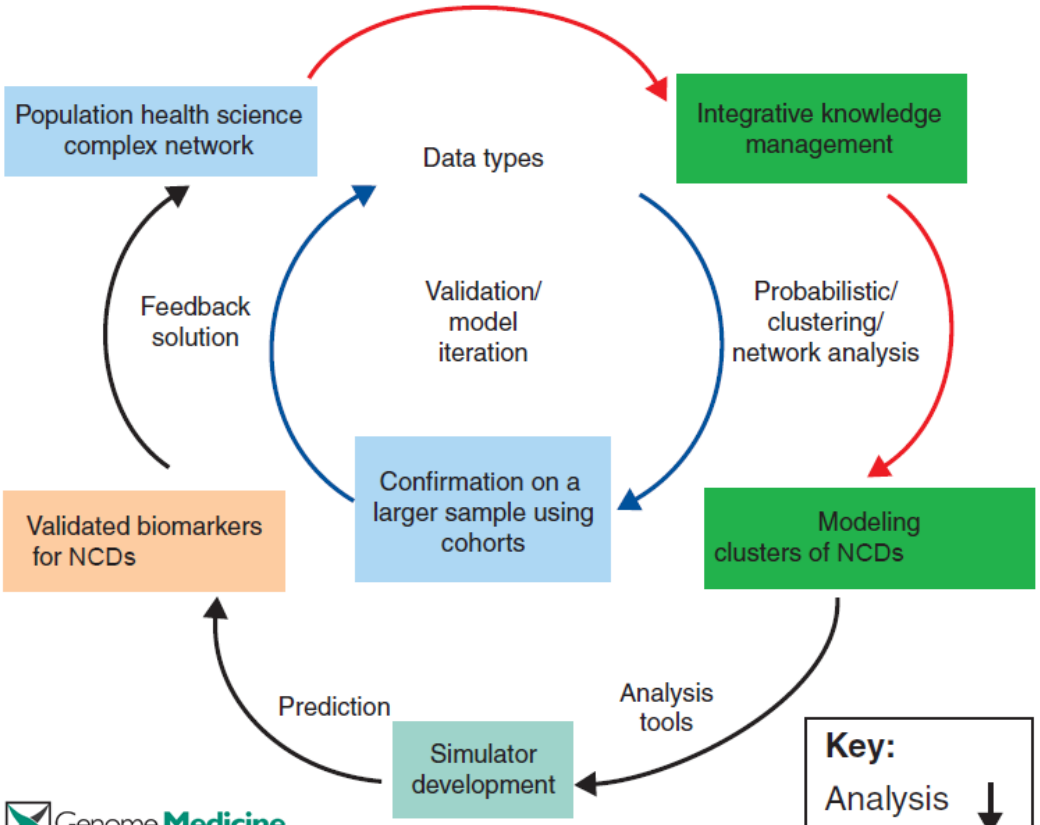




From retrospective personalized to prospective personalized medicine



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

Genome Medicine

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Systems medicine and integrated care to combat chronic noncommunicable diseases