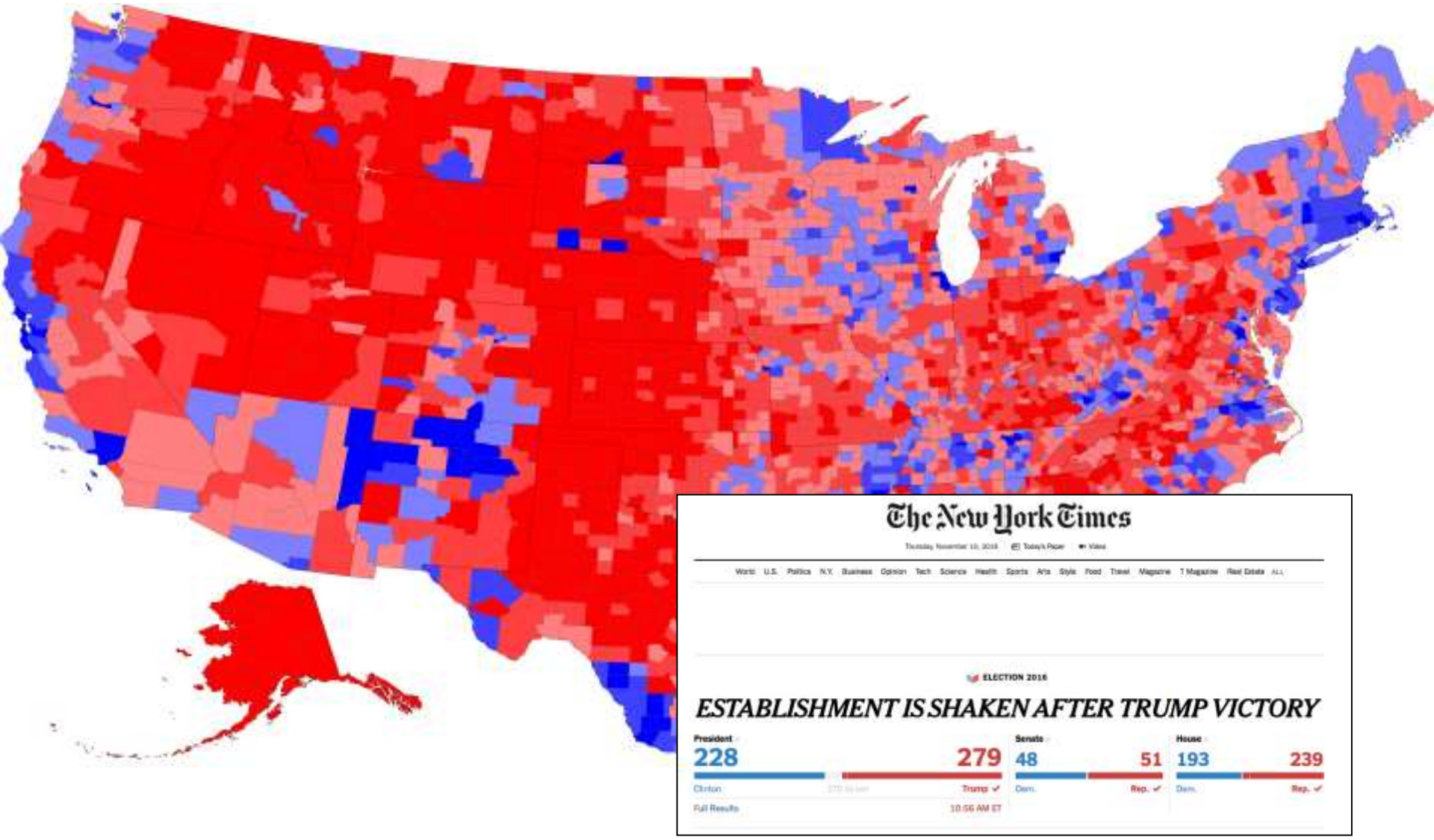
Will precision medicine improve population health?

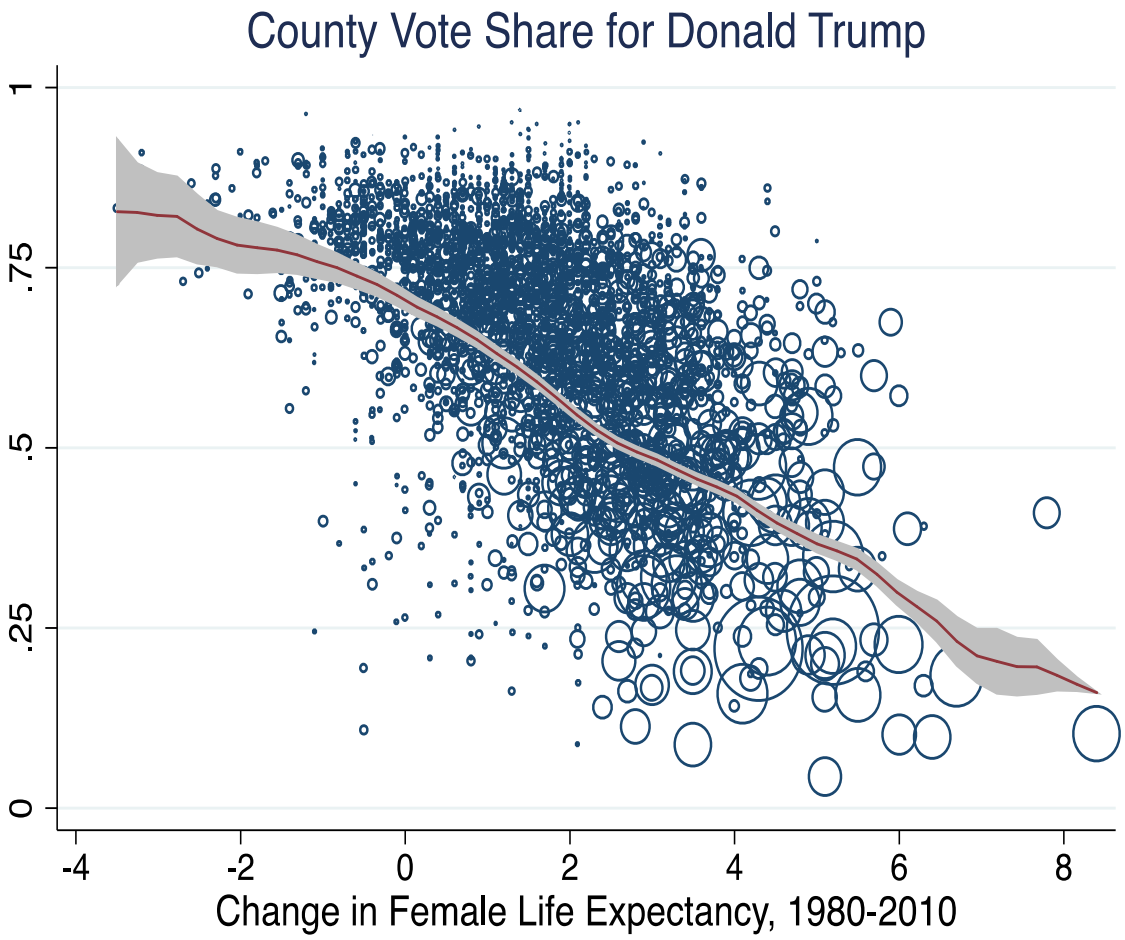
Sandro Galea

Boston University School of Public Health

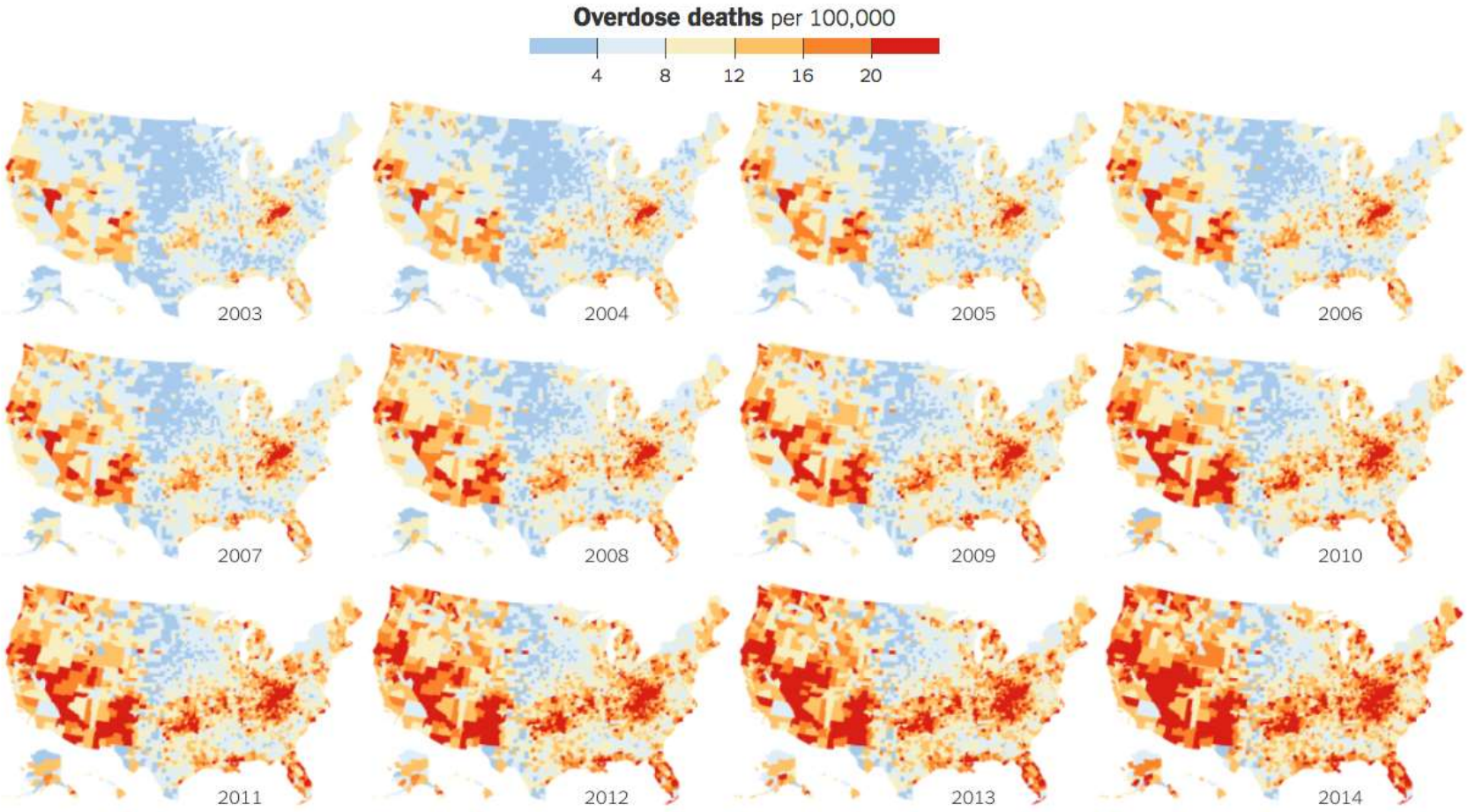
Why does this even matter?



http://3.bp.blogspot.com/-phwaYLl6iGM/UJw2ZsdFahI/AAAAAAAAAj8/wg0bSIOhhnI/s1600/electoral-small.png



Slide courtesy of Jacob Bor



Park H & Block M. How the epidemic of drug overdose deaths ripples across America. The *New York Times* January 19, 2016. http://www.nytimes.com/interactive/2016/01/07/us/drug-overdose-deaths-in-the-us.html.

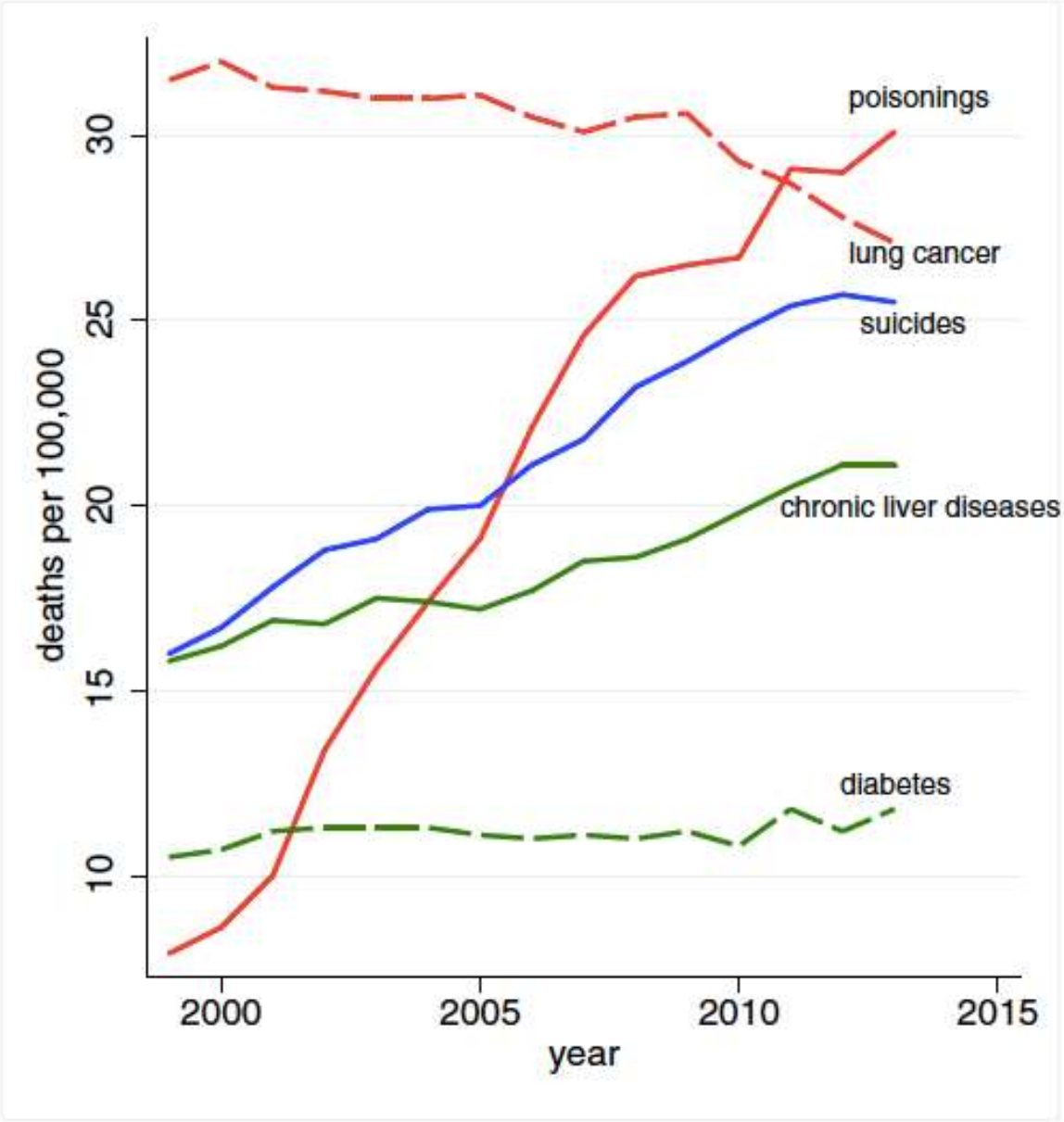


Fig. 2. Mortality by cause, white non-Hispanics ages 45–54.

Case A, Deaton A. Rising morbidity and mortality in midlife among white non-Hispanic Americans in the 21st century.PNAS. 112(49); 15078–15083, doi: 10.1073/pnas.1518393112.

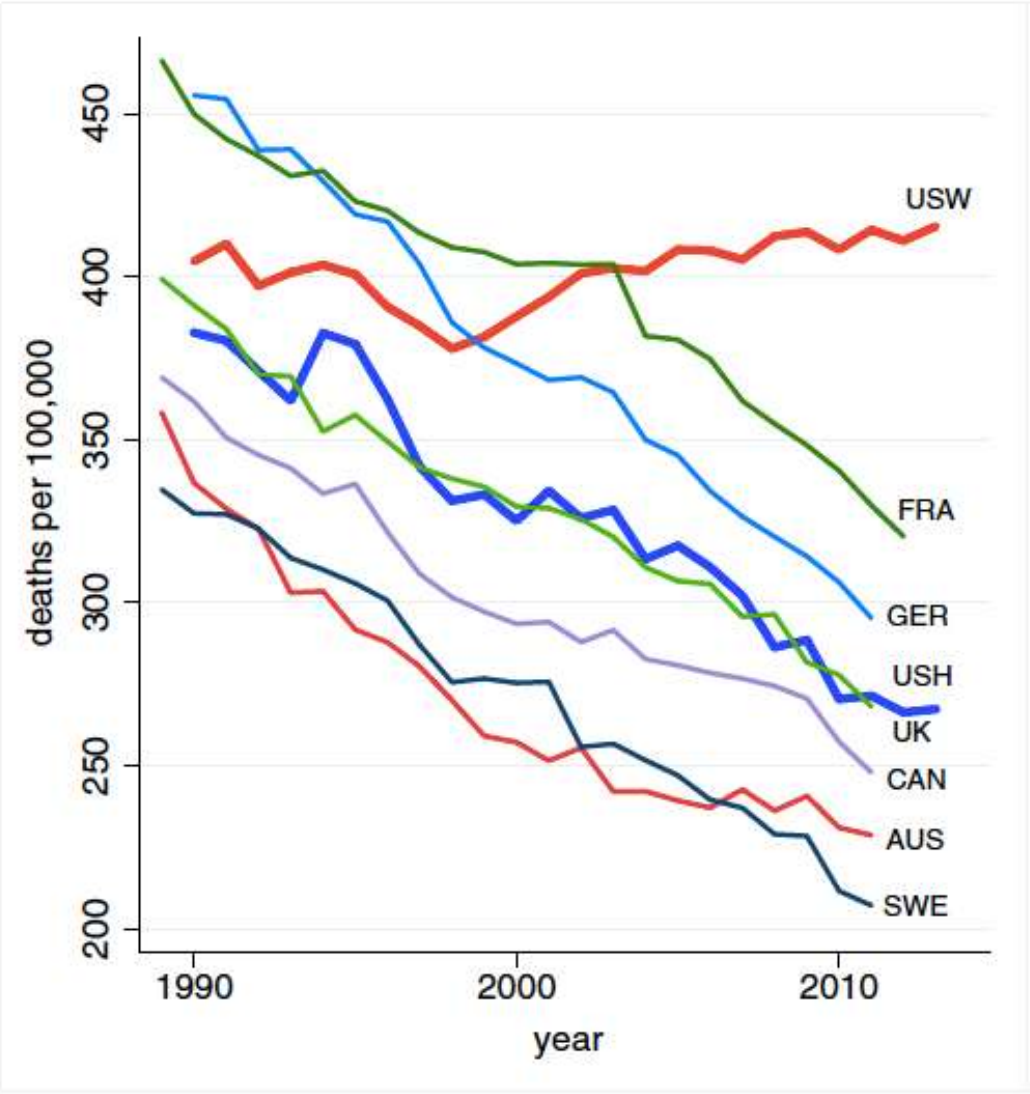


Fig. 1. All-cause mortality, ages 45–54 for US White non-Hispanics (USW), US Hispanics (USH), and six comparison countries: France (FRA), Germany (GER), the United Kingdom (UK), Canada (CAN), Australia (AUS), and Sweden (SWE).

Case A, Deaton A. Rising morbidity and mortality in midlife among white non-Hispanic Americans in the 21st century.PNAS. 112(49); 15078–15083, doi: 10.1073/pnas.1518393112.

What the health conversation has been recently

Revista Española de Enfermedades Digestivas

Rev Esp Enferm D
Vol. 102, N.° 10, pp. 573-

The NE

Personalized medicine: inevitable

Perspective

JULY 22, 2010

The Path to Personalized Medicine

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

Major investments in basic science have created
an opportunity for significant progress in
clinic
hund

the NIH and the FDA will invest
in advancing translational and

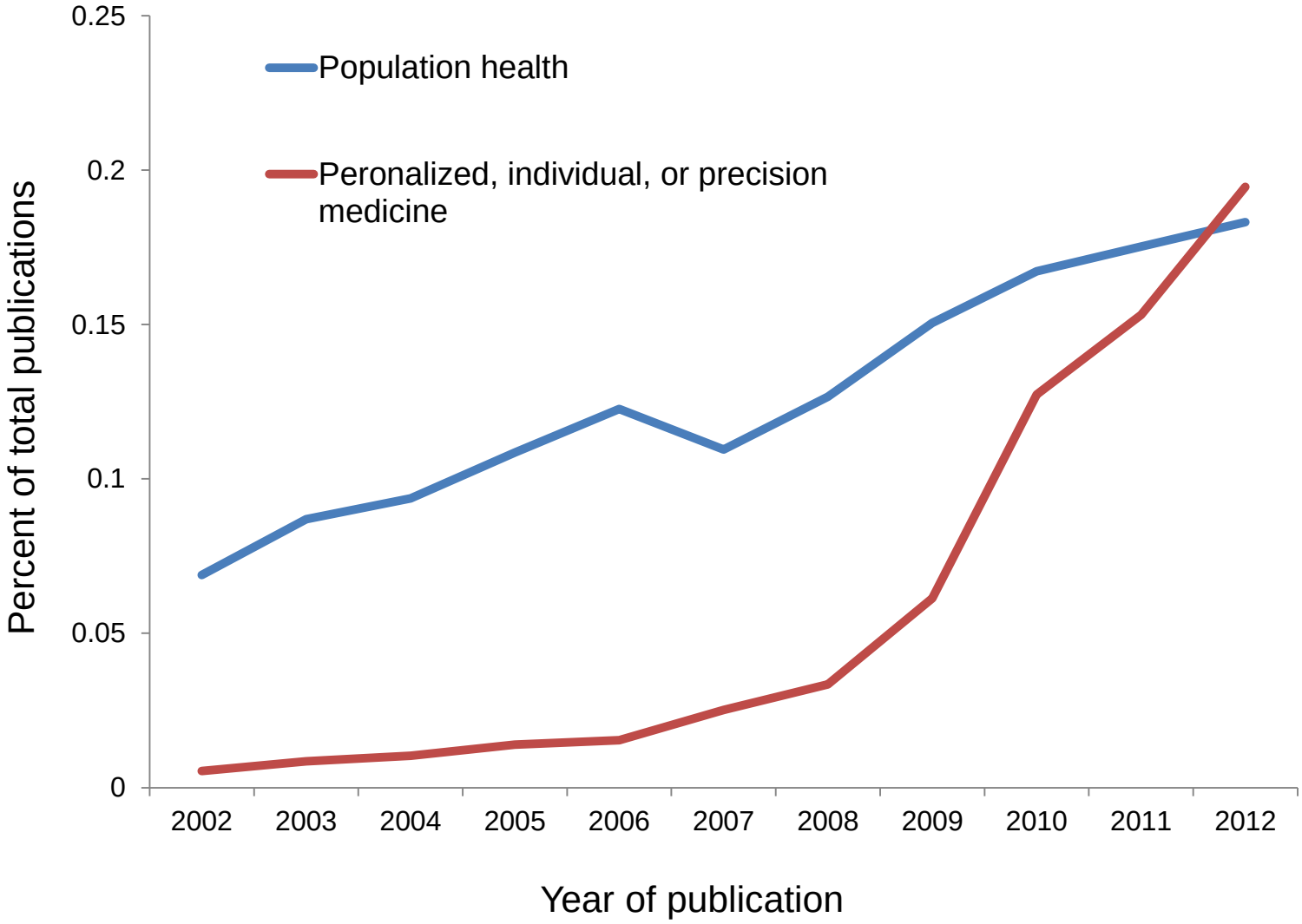
Journal of Diabetes Science and Technology
Volume 3, Issue 4, July 2009

SYMPOSIUM

The Case for Personalized Medicine

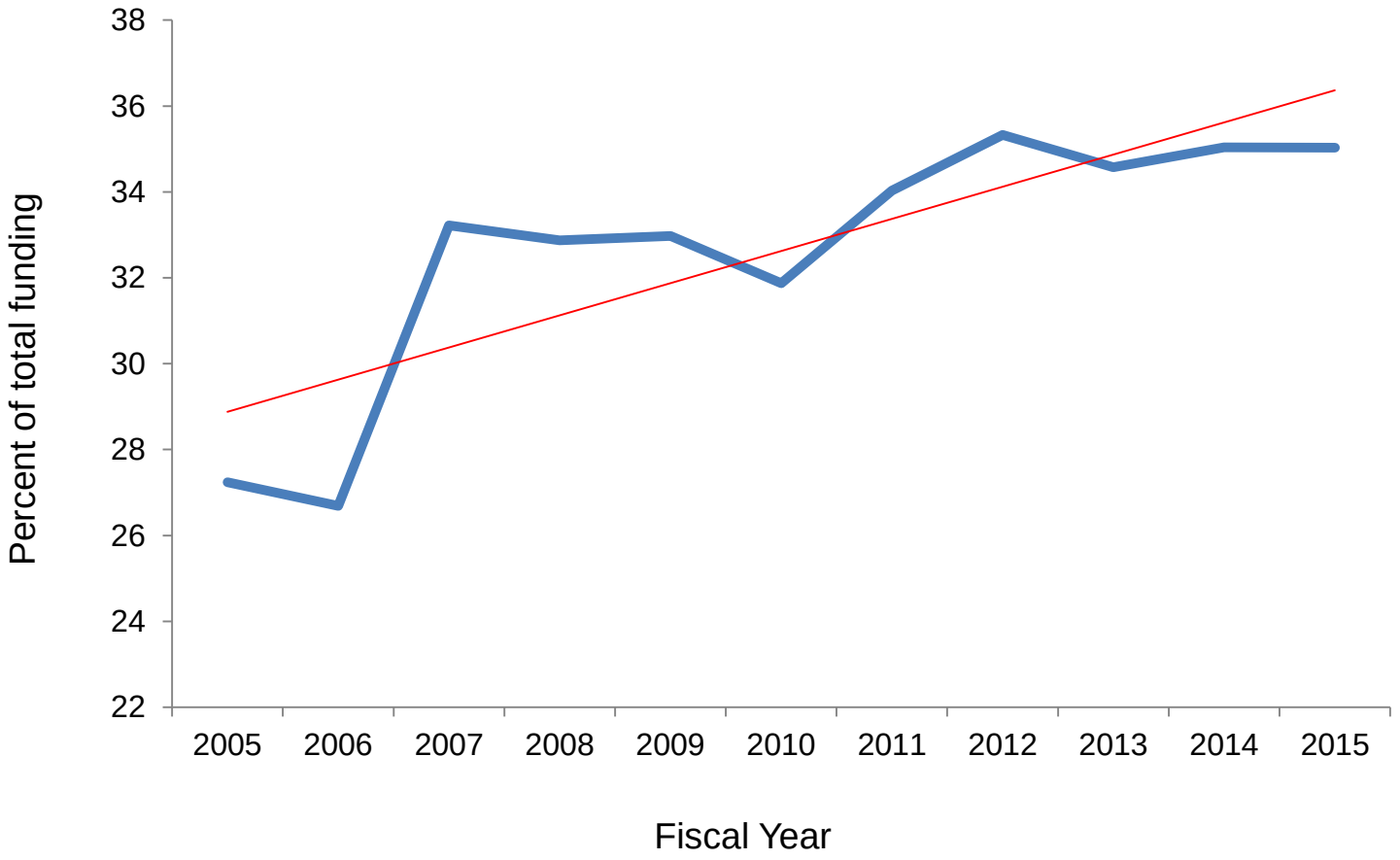
Edward Abrahams, Ph.D.,[1] and Mike Silver, Ph.D.[2]

Proportion of papers in PubMed, 2002 - 2012



PubMed search results for “population health” and "Individualized Medicine" or "personalized medicine" or "personalised medicine" or “individual medicine” or “precision medicine” from 2002-2012. <http://www.ncbi.nlm.nih.gov/> Accessed November 20, 2014.

Proportion of NIH funding awarded to projects with the terms “genetic” or “genetics” in the title, abstract or terms



NIH RePORTER. Search results for projects for which funding data is available. <http://projectreporter.nih.gov/reporter.cfm> Accessed on November 20, 2014.

The loyal opposition

to the aspirations of science

The loyal opposition

to compelling ideas that do not advance health

The loyal opposition

There is one question that matters. Will precision approaches improve population health?

It depends.

No, unless.

Three reasons why not.

1. The challenges of complexity in biology

Genes matter relatively little

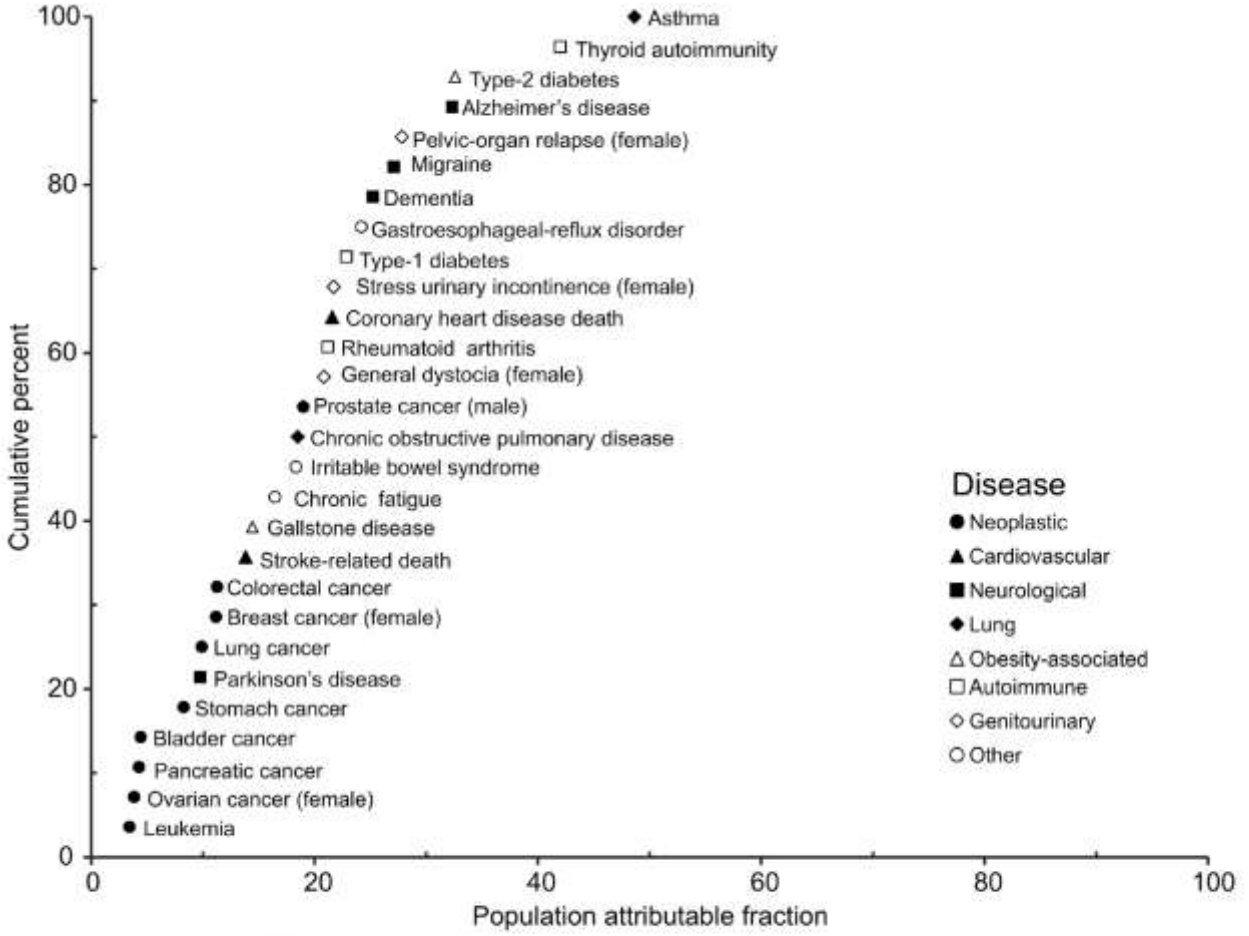
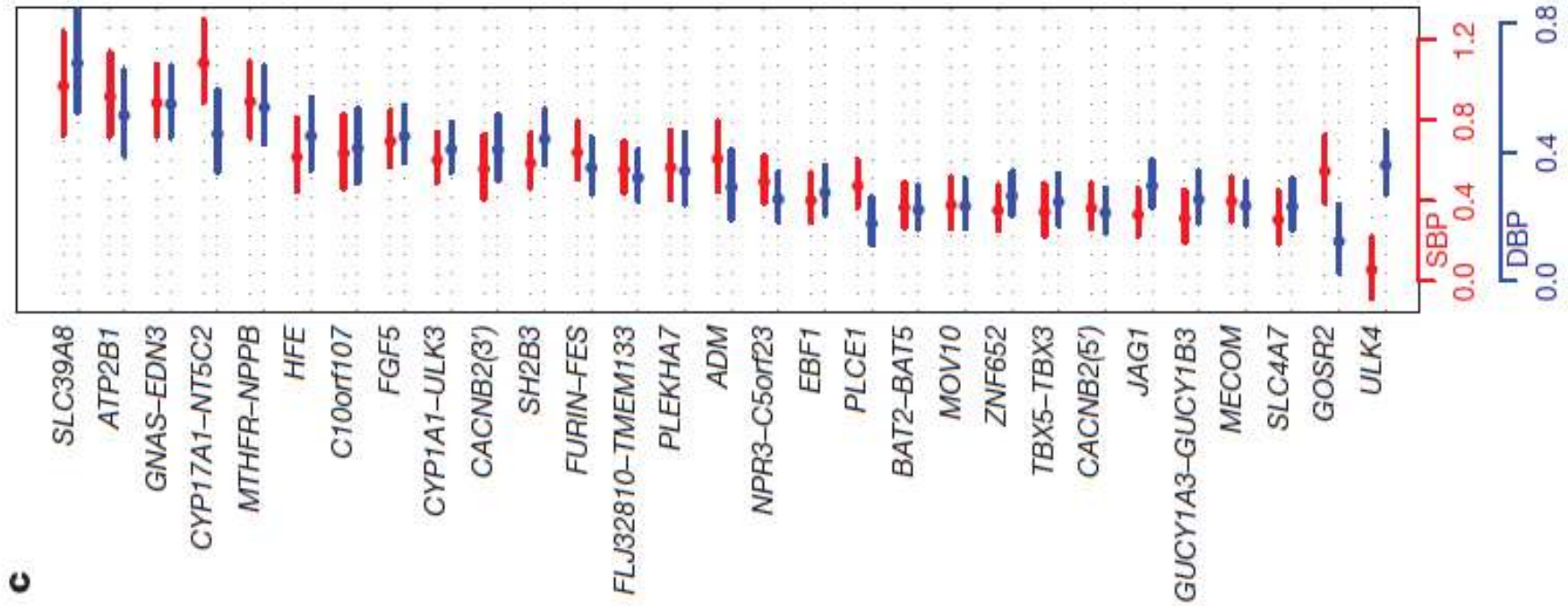


Fig 1. Population attributable fractions (PAFs) for 28 disease phenotypes estimated from studies of monozygotic twins. Sources of data and statistics are summarized in Table 2.

doi:10.1371/journal.pone.0154387.g001

Many variants, with very small effect



Little evidence for efficacy of molecular targeting

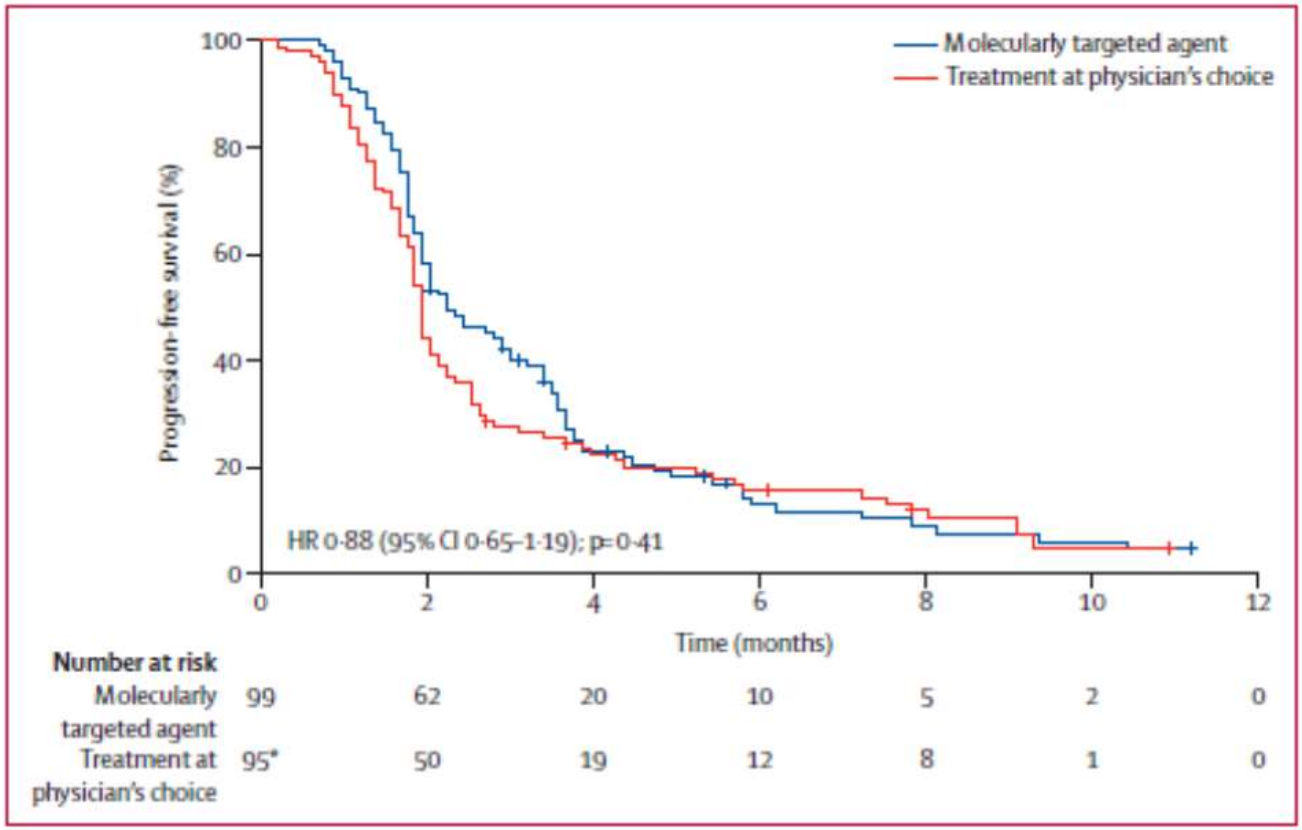
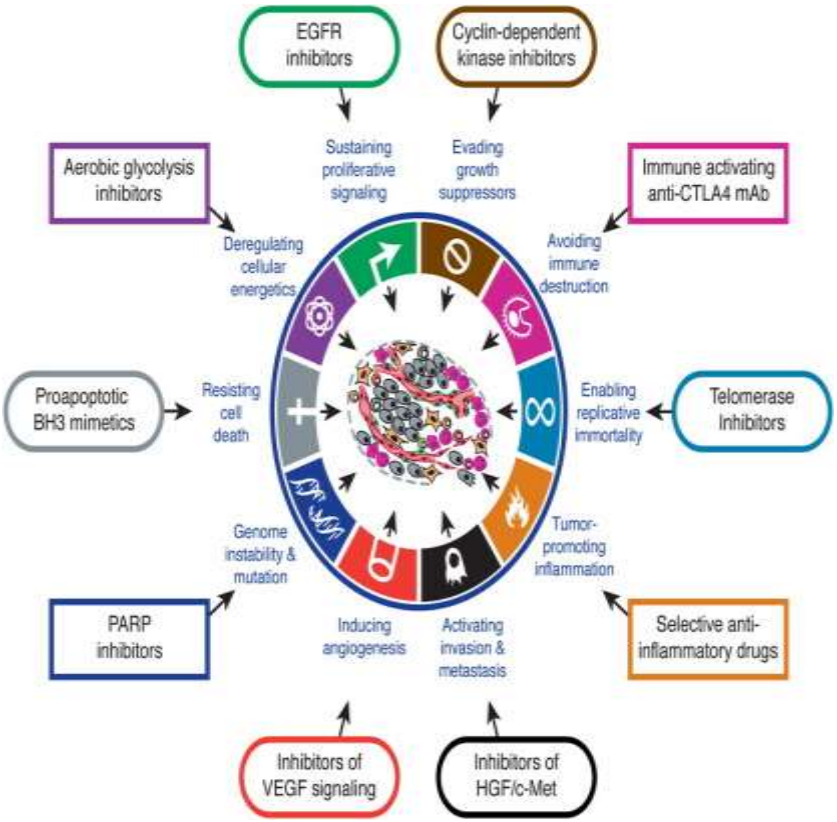


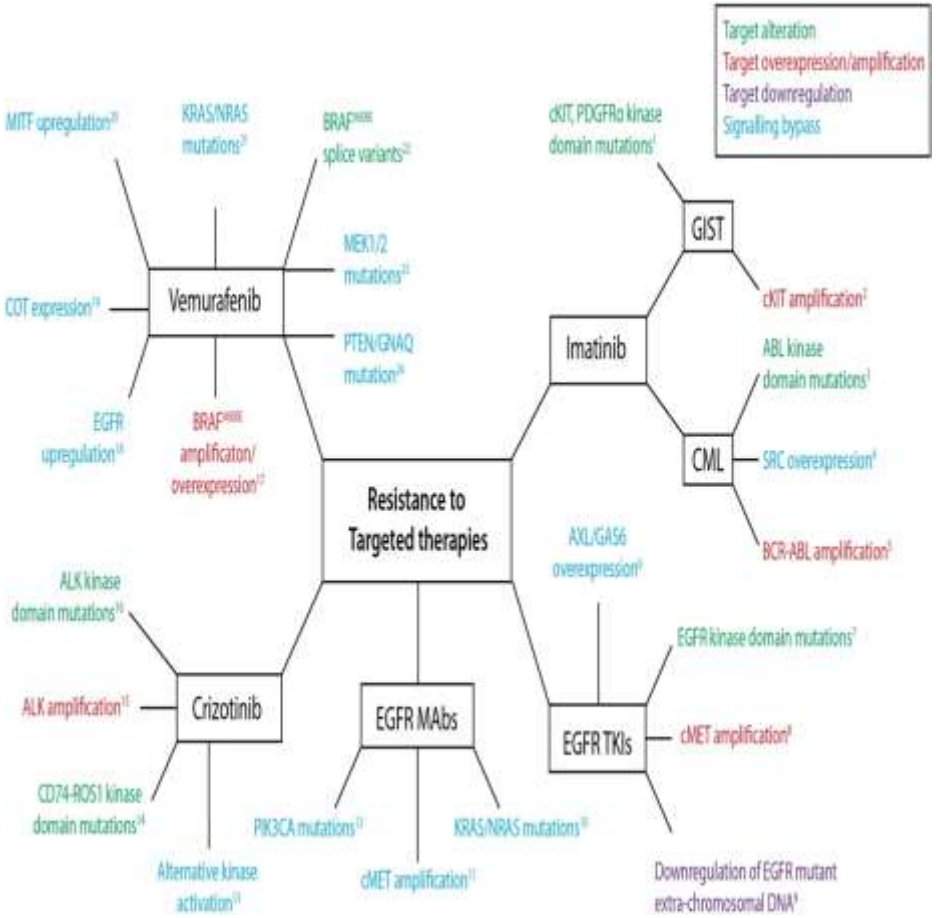
Figure 3: **Progression-free survival**

*One patient had a follow-up of zero days so is not shown here.

Le Tourneau et al, Lancet Onc 2015

Multimechanism diseases with predictable resistance



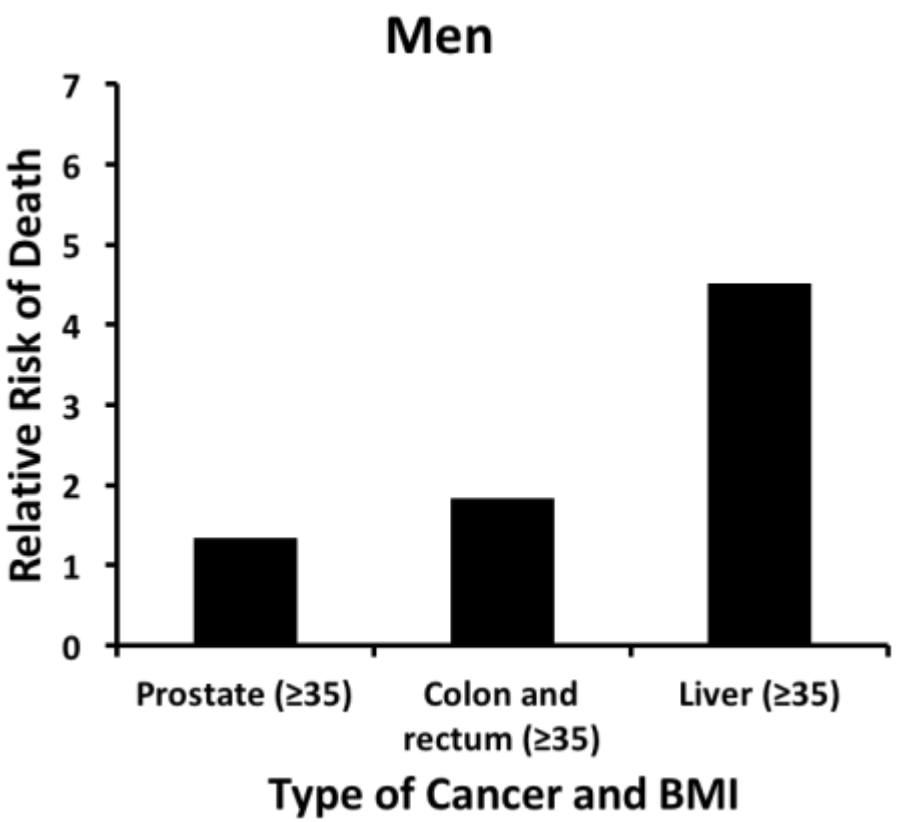


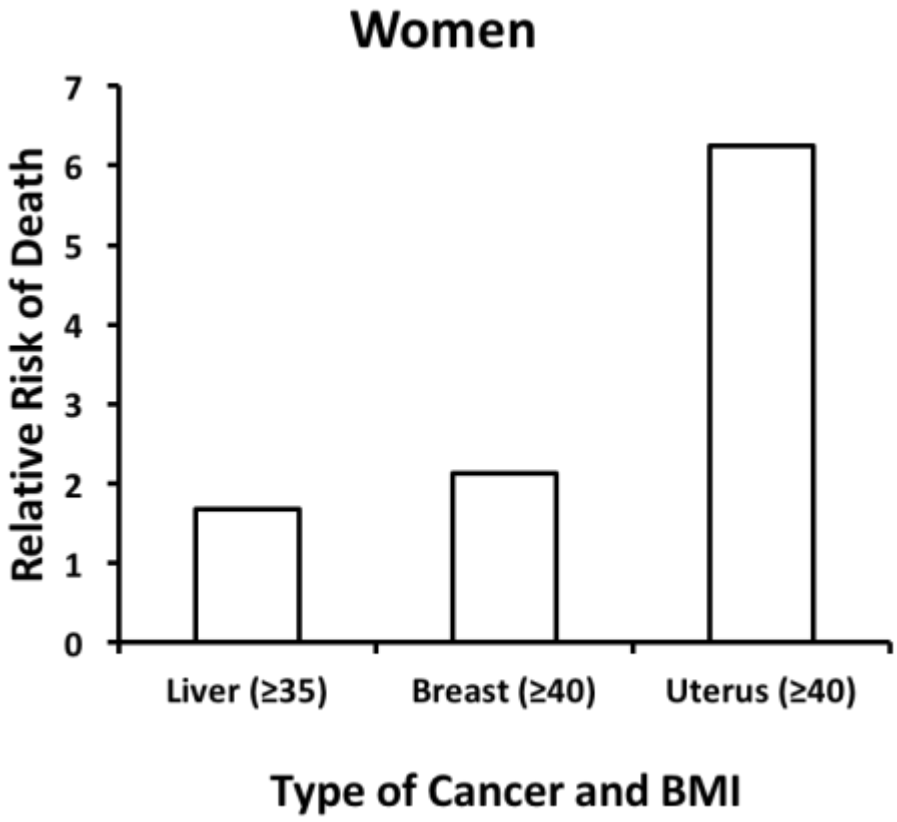
Hanahan D, Weinberg R. Cell 2011; 144: 646-774

Burrell RA, Swanton C. Mol Oncol 2014; 8: 1095-1111

Slide courtesy of Michael Fernandes

The inevitable overwhelming role of behavior

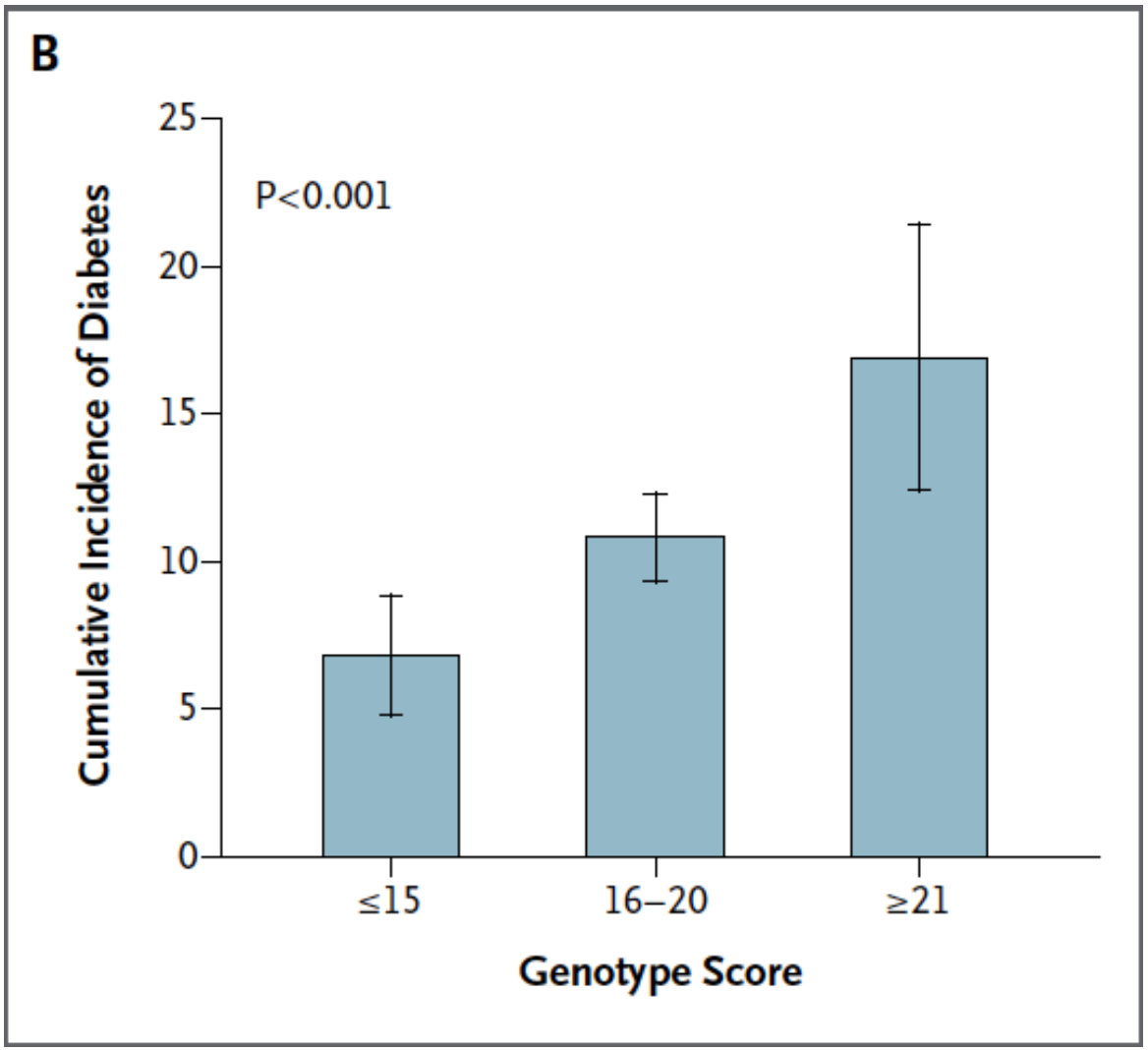




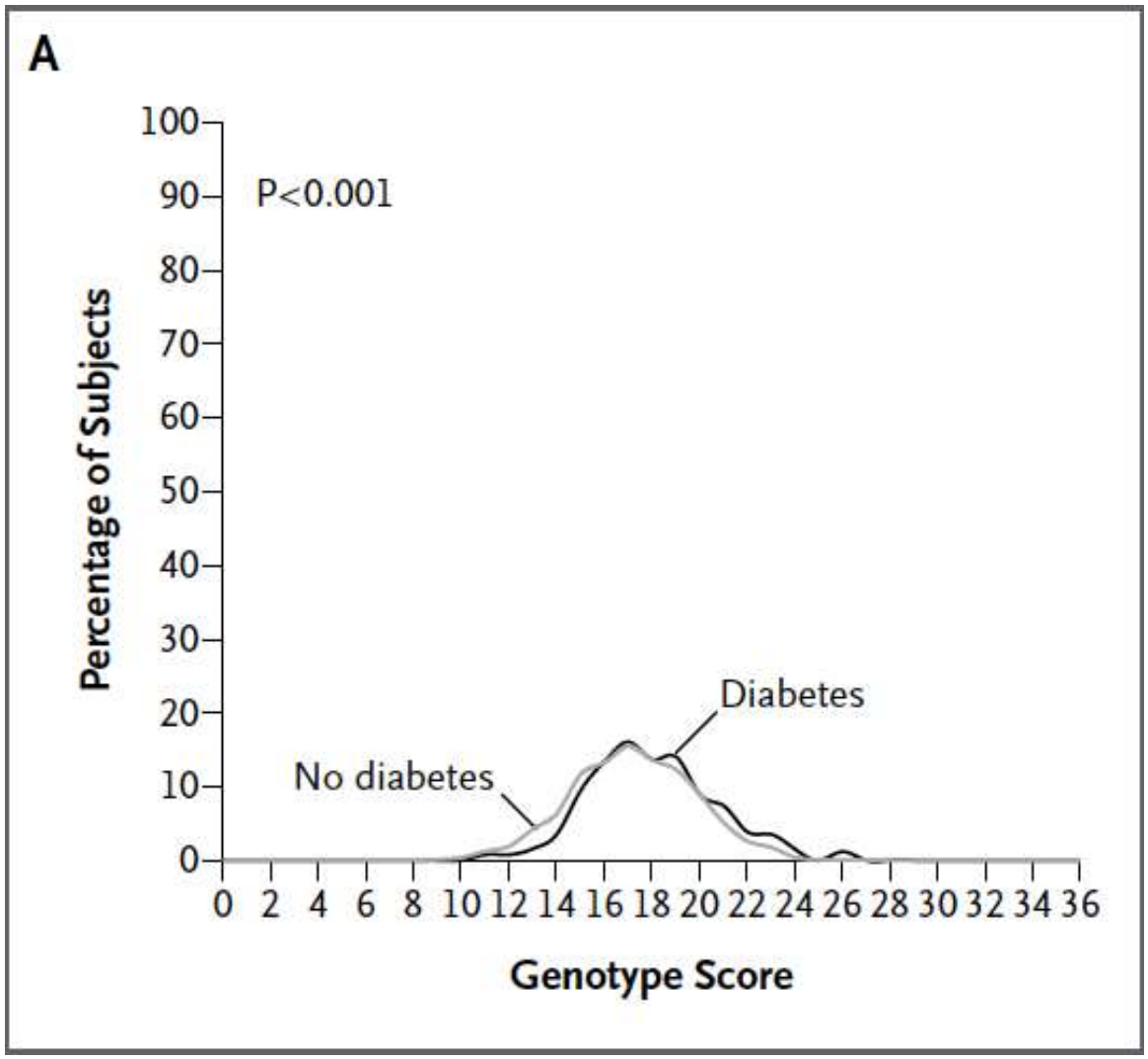
Calle et al. N. Engl. J. Med. 2003; 348: 1625-1638

Slide courtesy of Michael Joyner

2. The conflation of the individual and population



Meigs JB, Shrader P, Sullivan LM, McAteer JB, Fox CS, Dupuis J, Manning AK, Florez JC, Wilson PW, D'Agostino RB Sr, Cupples LA. Genotype score in addition to common risk factors for prediction of type 2 diabetes. N Engl J Med. 2008 Nov 20;359(21):2208-19



Meigs JB, Shrader P, Sullivan LM, McAteer JB, Fox CS, Dupuis J, Manning AK, Florez JC, Wilson PW, D'Agostino RB Sr, Cupples LA. Genotype score in addition to common risk factors for prediction of type 2 diabetes. N Engl J Med. 2008 Nov 20;359(21):2208-19

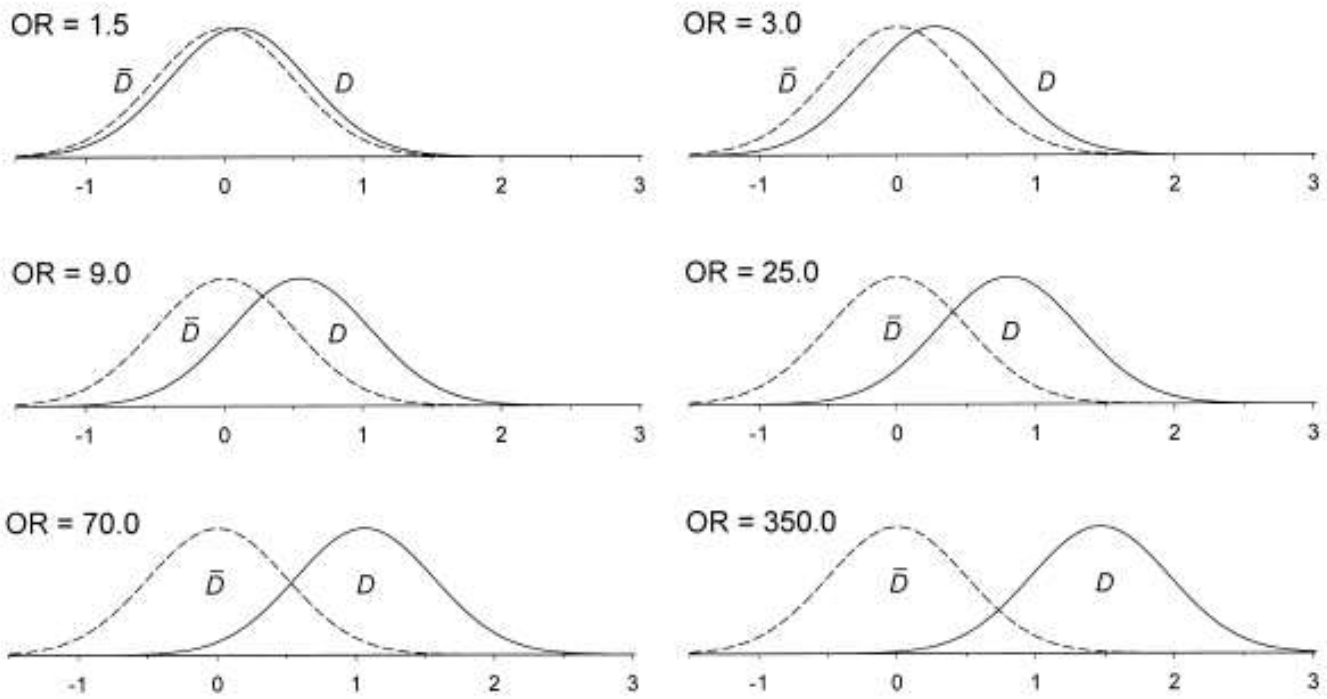
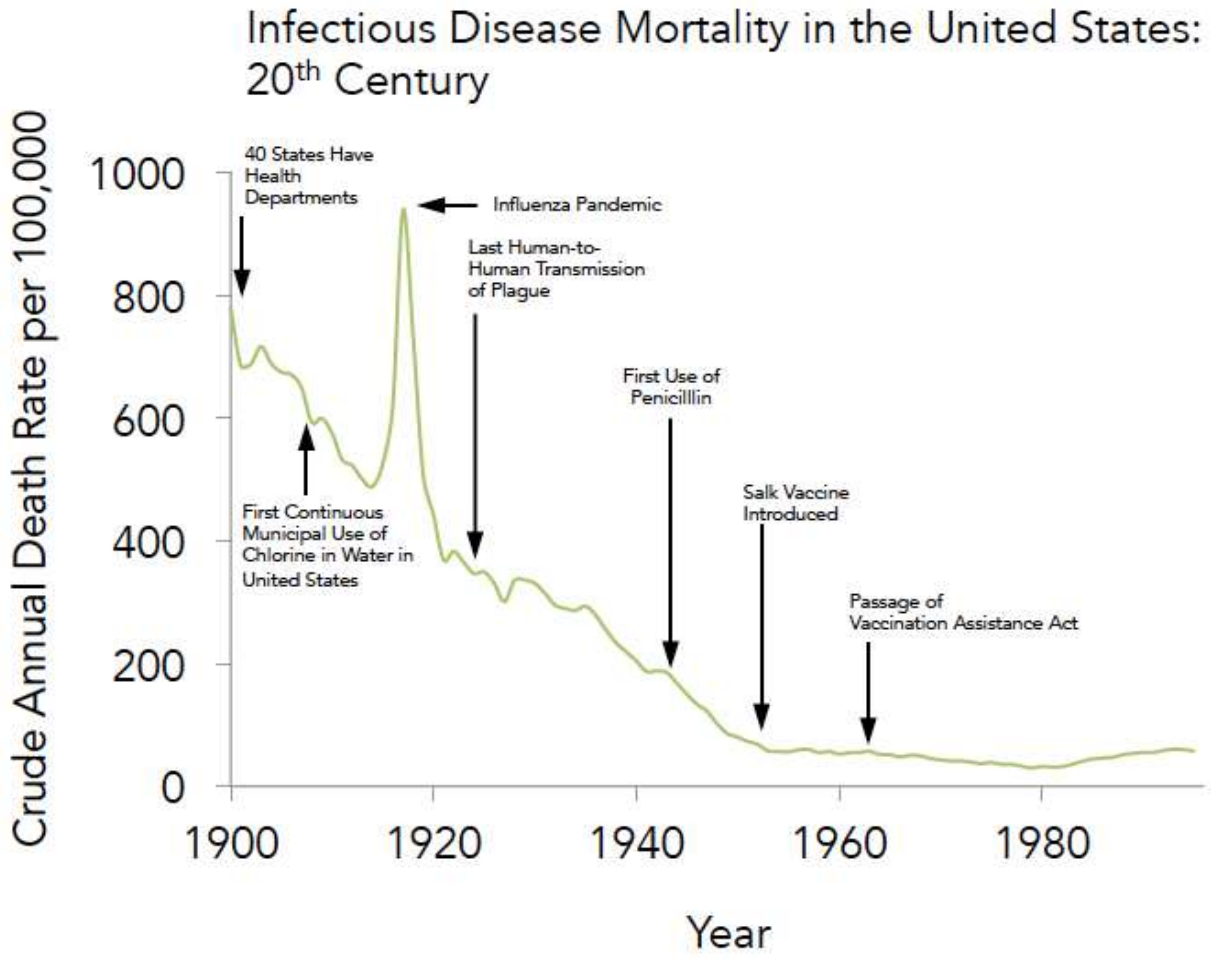
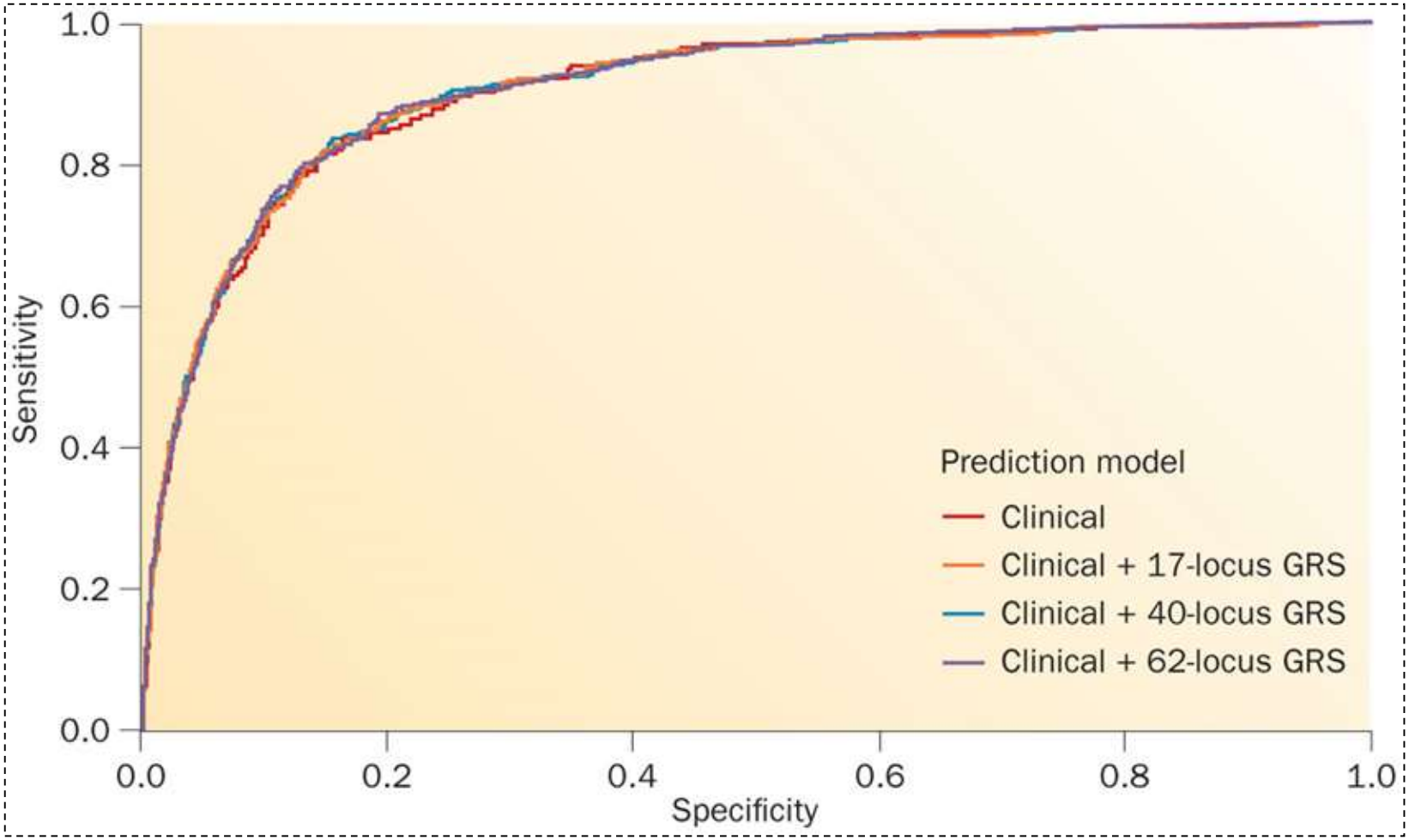


FIGURE 2. Probability distributions of a marker, X, in cases (solid curves) and controls (dashed curves) consistent with the logistic model $\text{logit}P(D = 1|X) = \alpha + \beta X$. It has been assumed that X has a mean of 0 and a standard deviation of 0.5 in controls so that a unit increase represents the difference between the 84th and 16th percentiles of X in controls. The marker is normally distributed, with the same variance in cases. The odds ratio (OR) per unit increase in X is shown.

Pepe MS, Janes H, Longton G, Leisenring W, Newcomb P. Limitations of the odds ratio in gauging the performance of a diagnostic, prognostic, or screening marker. American Journal of Epidemiology 2004; 159:882-890.


Infectious Disease Mortality in the United States: 20th Century
Crude Annual Death Rate per 100,000
1000
800
600
400
200
0
1900
1920
1940
1960
1980
Year
40 States Have Health Departments
Influenza Pandemic
Last Human-to-Human Transmission of Plague
First Use of Penicilllin
Salk Vaccine Introduced
Passage of Vaccination Assistance Act
First Continuous Municipal Use of Chlorine in Water in United States

Predicting diabetes



Hivert MF et al. Nat Rev Endocrinol, 2014; slide courtesy of Michael Joyner.

3. The fallacy of individual behavior change

The impact of communicating genetic risks of disease on risk-reducing health behaviour: systematic review with meta-analysis

Gareth J Hollands,[1] David P French,[2] Simon J Griffin,[3] A Toby Prevost,[4] Stephen Sutton,[3] Sarah King,[1] Theresa M Marteau[1]

[1]Behaviour and Health Research Unit, University of Cambridge, Cambridge, UK
[2]School of Psychological Sciences, University of Manchester, Manchester, UK
[3]Department of Public Health and Primary Care, University of Cambridge, Cambridge, UK
[4]Imperial Clinical Trials Unit, Imperial College London, London, UK

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http://dx.doi.org/10.1136/bmj.i1102

Accepted: 14 February 2016

ABSTRACT

OBJECTIVE

To assess the impact of communicating DNA based disease risk estimates on risk-reducing health behaviours and motivation to engage in such behaviours.

DESIGN

Systematic review with meta-analysis, using Cochrane methods.

DATA SOURCES

Medline, Embase, PsycINFO, CINAHL, and the Cochrane Central Register of Controlled Trials up to 25 February 2015. Backward and forward citation searches were also conducted.

STUDY SELECTION

Randomised and quasi-randomised controlled trials involving adults in which one group received personalised DNA based estimates of disease risk for conditions where risk could be reduced by behaviour change. Eligible studies included a measure of risk-reducing behaviour.

RESULTS

We examined 10 515 abstracts and included 18 studies that reported on seven behavioural outcomes, including smoking cessation (six studies; n=2663), diet (seven studies; n=1784), and physical activity (six studies; n=1704). Meta-analysis revealed no significant effects of communicating DNA based risk estimates on smoking cessation (odds ratio 0.92, 95% confidence interval 0.63 to 1.35, P=0.67), diet (standardised mean difference 0.12, 95% confidence interval −0.00 to 0.24, P=0.05), or physical activity (standardised mean difference −0.03, 95% confidence interval −0.13 to 0.08, P=0.62). There were also no effects on any other behaviours (alcohol use, medication use, sun protection behaviours, and attendance at screening or behavioural support programmes) or on motivation to change behaviour, and no adverse effects, such as depression and anxiety. Subgroup analyses provided no clear evidence that communication of a risk-conferring genotype affected behaviour more than communication of the absence of such a genotype. However, studies were predominantly at high or unclear risk of bias, and evidence was typically of low quality.

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.

SYSTEMATIC REVIEW REGISTRATION

This is a revised and updated version of a Cochrane review from 2010, adding 11 studies to the seven previously identified.

WHAT IS ALREADY KNOWN ON THIS TOPIC

Genetic testing is being increasingly used in a growing number of healthcare settings and in direct-to-consumer testing for a range of common complex disorders

There is an expectation that communicating DNA based disease risk estimates will motivate changes in key health behaviours, including smoking, diet, and physical activity

There is a need for a rigorous systematic review to examine whether communicating genetic risks does indeed motivate risk-reducing behaviour change

WHAT THIS STUDY ADDS

The results of this updated systematic review with meta-analysis using Cochrane methods suggest that communicating DNA based disease risk estimates has little or no impact on risk-reducing health behaviour

Existing evidence does not support expectations that such interventions could play a major role in motivating behaviour change to improve population health

Introduction

Searching for gene variants associated with risks of common complex conditions, including diabetes and various cancers, continues to receive considerable attention.[1 2] Although the main target of such research is more effective treatments, more precise prediction of disease has also been anticipated. Less attention has been given to evaluating whether health benefits, in particular risk-reducing changes in behaviour, can be realised through communicating the results of such predictions. For example, does communicating to smokers that they have an increased genetic risk of developing lung cancer motivate smoking cessation, or does telling middle aged people that they have an increased genetic risk of developing diabetes motivate increased physical activity to reduce this risk? These are particularly timely questions, given high levels of interest in personalised medicine and in direct-to-consumer testing. More than 10 years ago, direct-to-consumer tests for a range of common complex disorders were rushed to market. These tests continue to be sold in Canada, the United Kingdom, and other European countries, including Denmark, Finland, the Netherlands, Sweden, and Ireland (www.23andme.com/en-gb/health/; www.23andme.com/en-eu/), with continued international expansion likely. In the United States, expansion was tempered in 2013 when the Food and Drug Administration ordered the company 23andme to stop selling its testing kits because of concerns about their accuracy and usefulness, but as of October 2015 the company has resumed selling some

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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

Expectations that communicating DNA based risk estimates changes behaviour is not supported by existing evidence

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There is a need for a rigorous systematic review to examine whether communicating genetic risks does indeed motivate risk-reducing behaviour change

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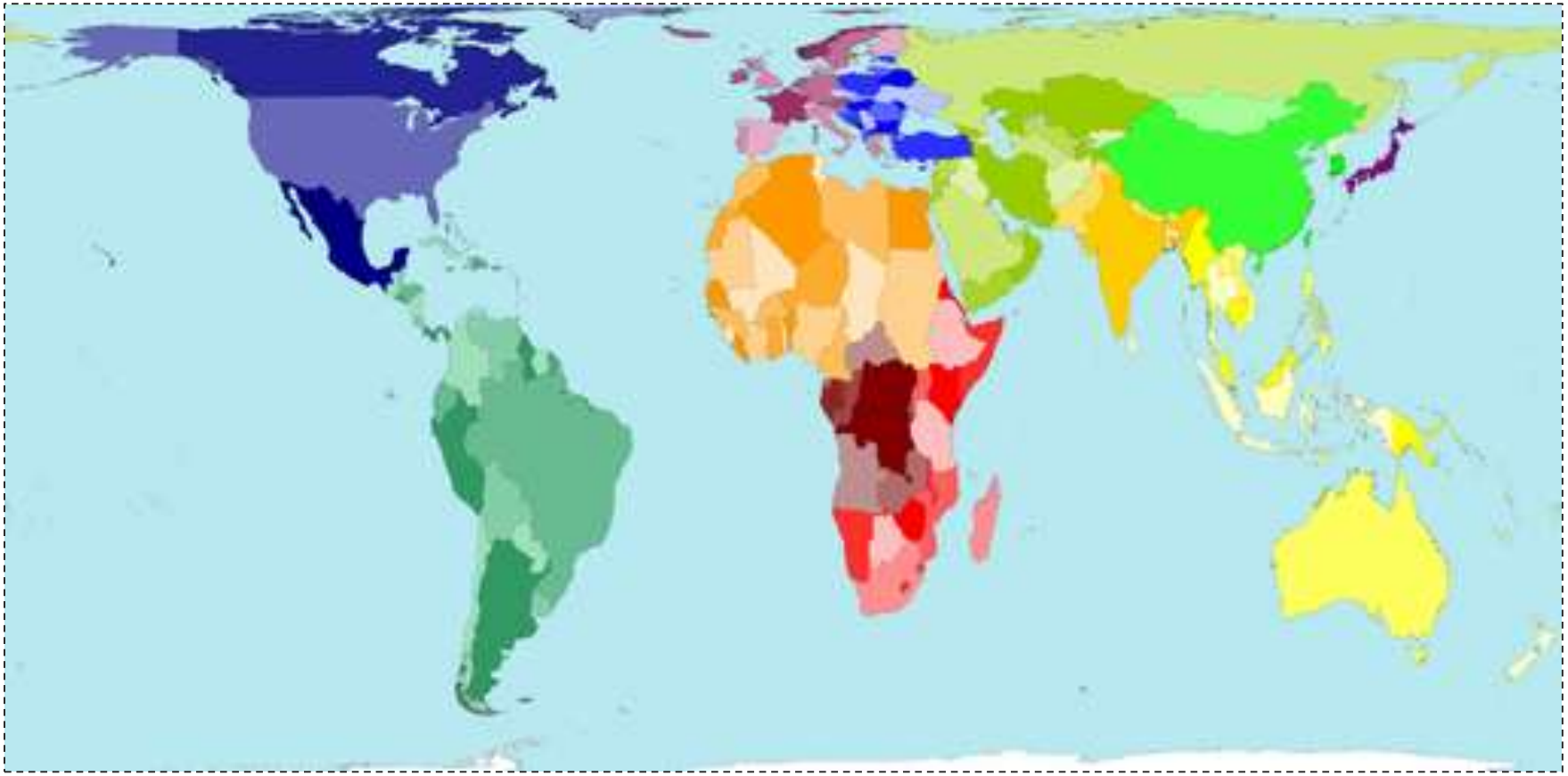
This discussion is not academic. Three reasons why it matters.

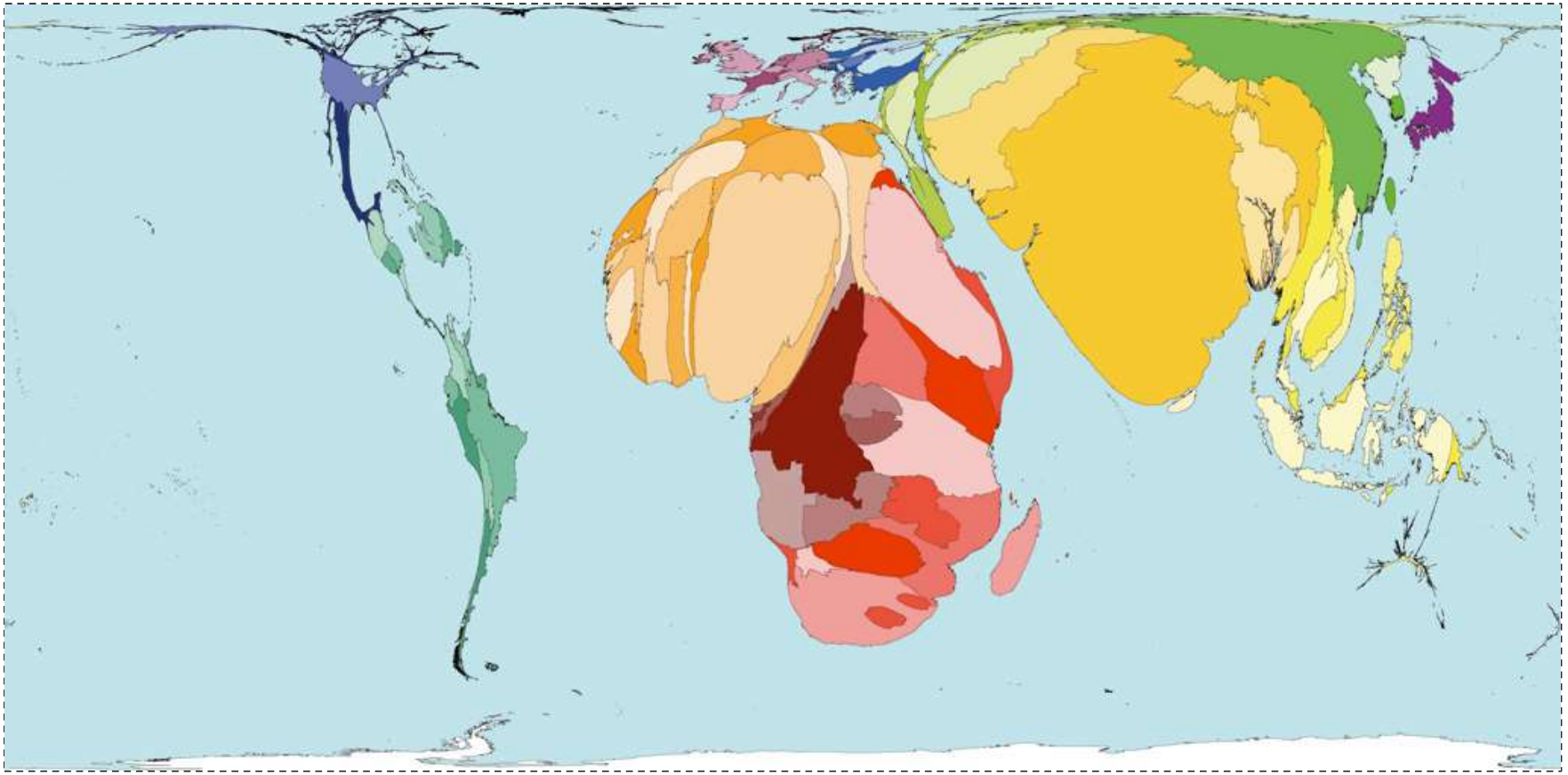
1. Missing the important, on compelling distraction

The world, actual size



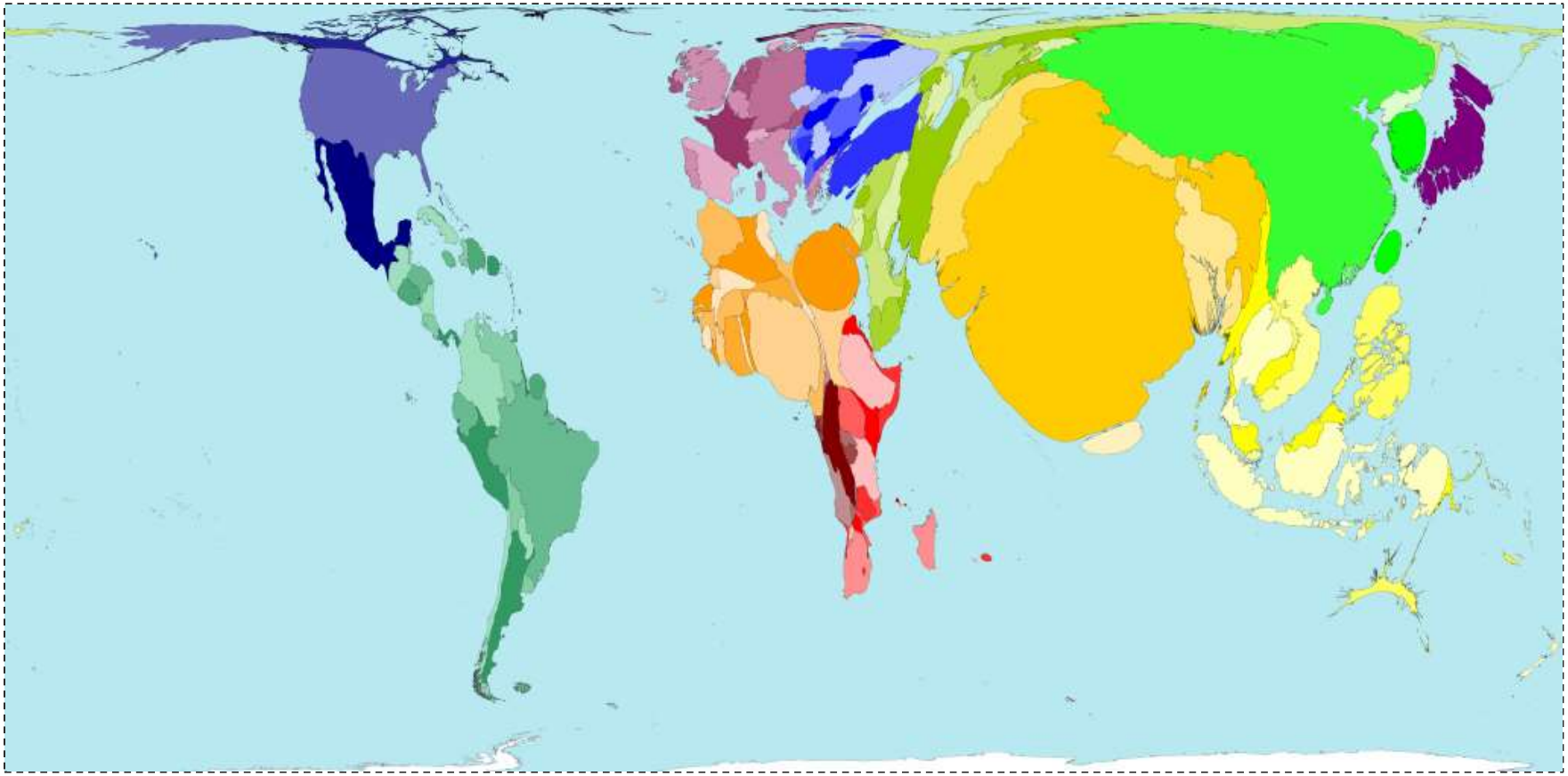
Worldmapper.<http://www.worldmapper.org/display.php?selected=1>

The world, by preventable deaths

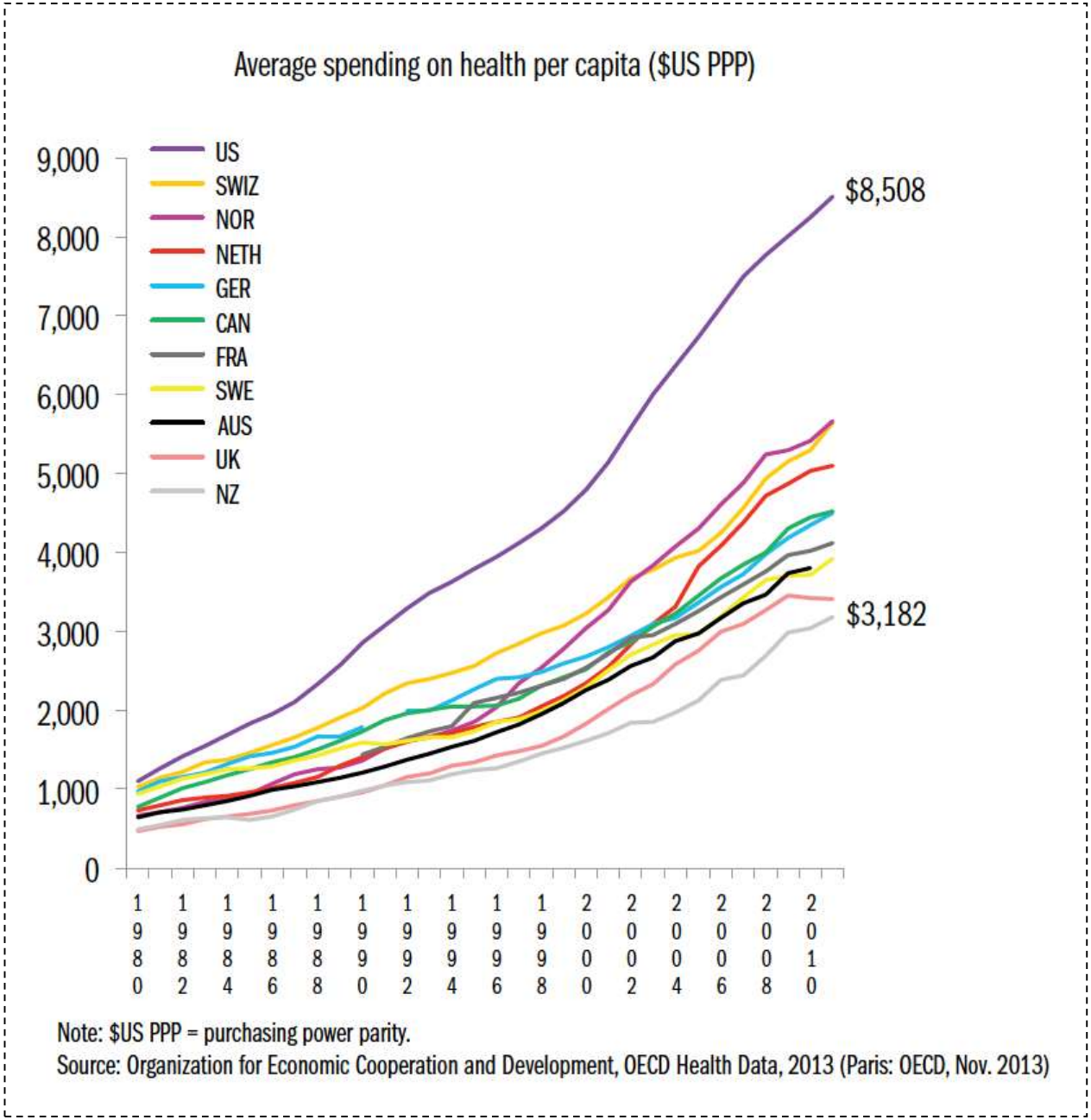


Worldmapper.<http://www.worldmapper.org/display.php?selected=1>

The world, by unhealthy life expectancy



Worldmapper.<http://www.worldmapper.org/display.php?selected=1>



http://www.commonwealthfund.org/~/media/files/publications/fund-report/2014/jun/1755_davis_mirror_mirror_2014.pdf

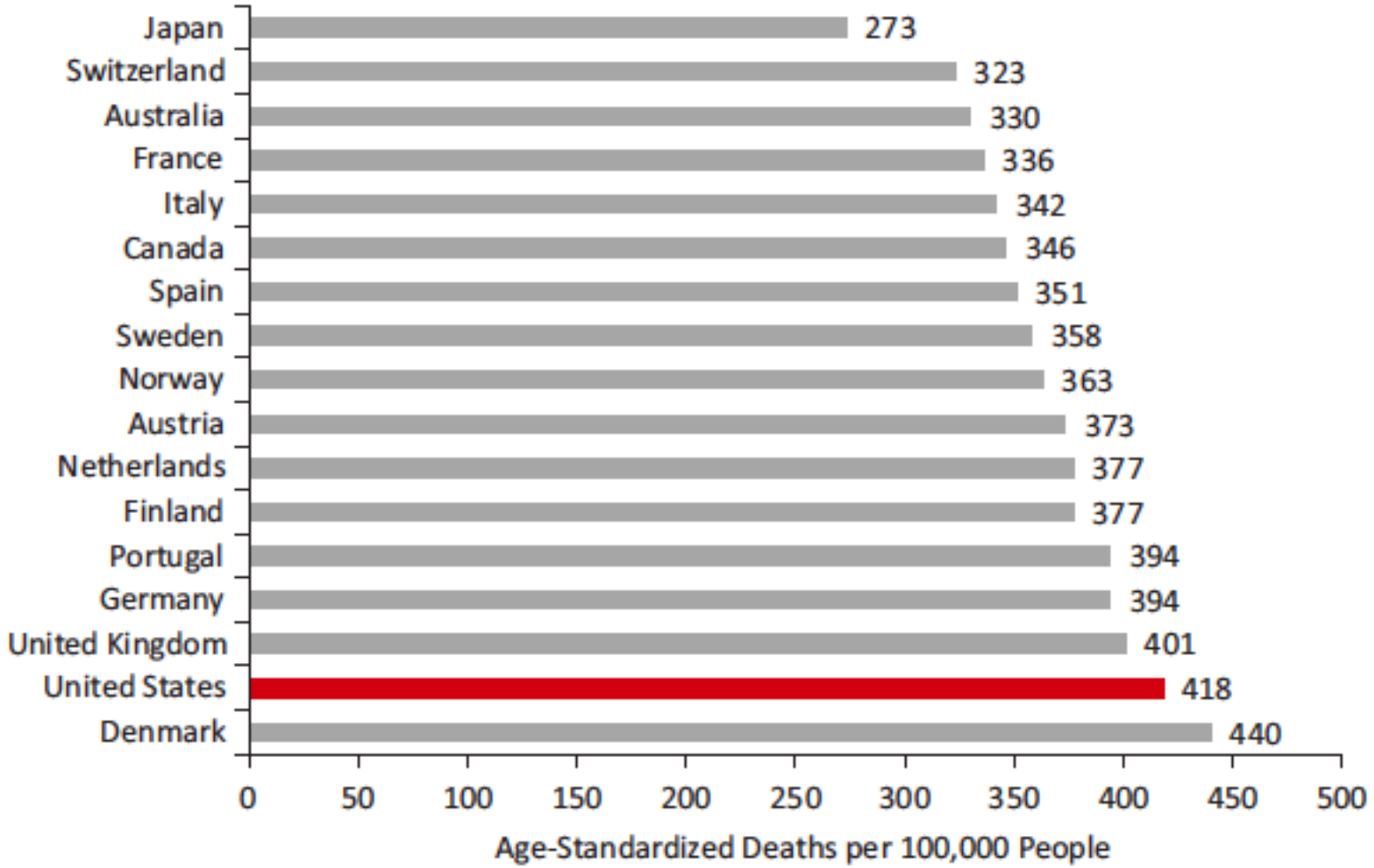


FIGURE 1-1 Mortality from noncommunicable diseases in 17 peer countries, 2008.
SOURCE: Data from World Health Organization (2011a, Table 3).

US Health in International Perspective. Shorter lives, poorer health. S Woolf, L Aron, eds. NRC and IOM. 2012.

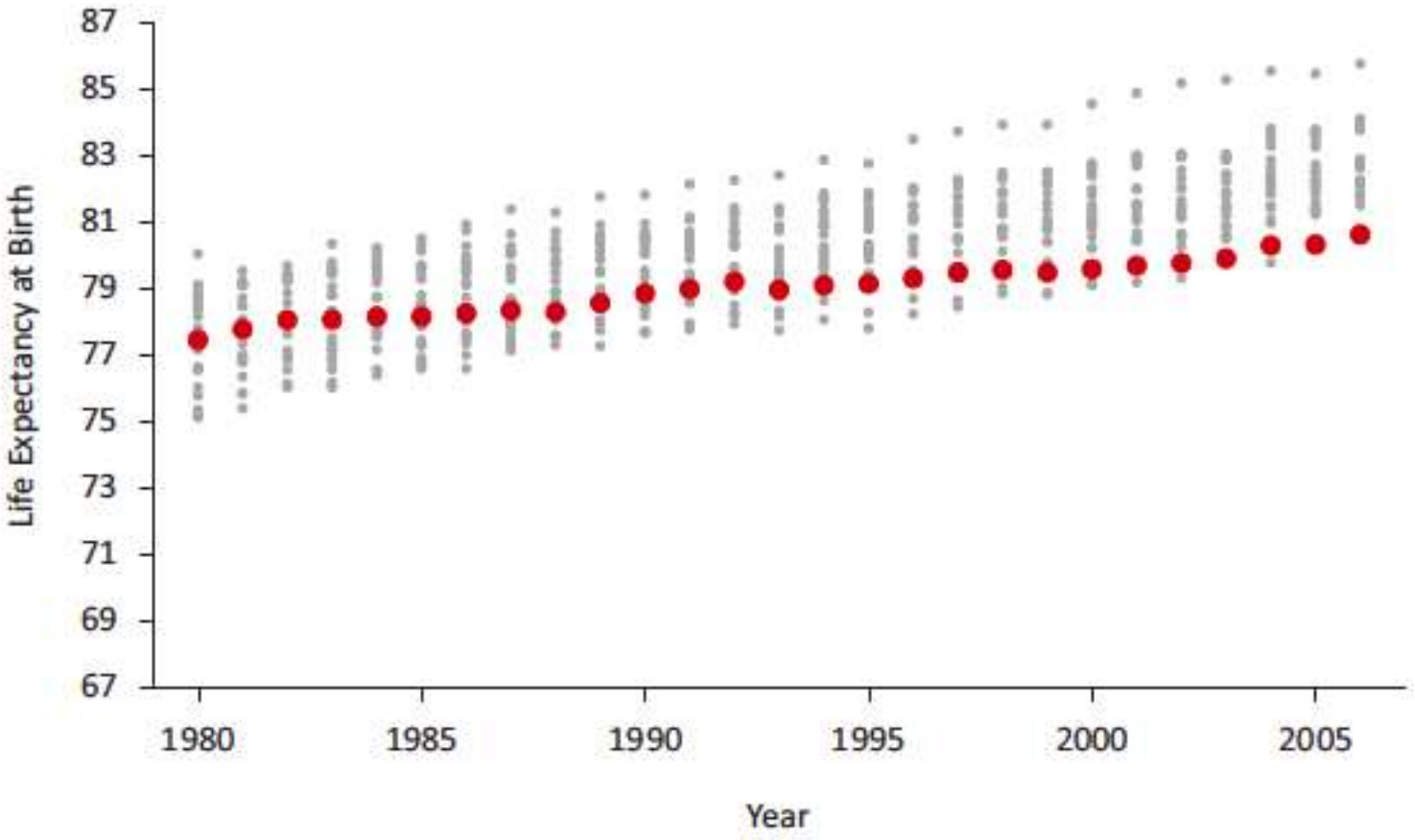


FIGURE 1-6 U.S. female life expectancy at birth relative to 21 other high-income countries, 1980-2006.

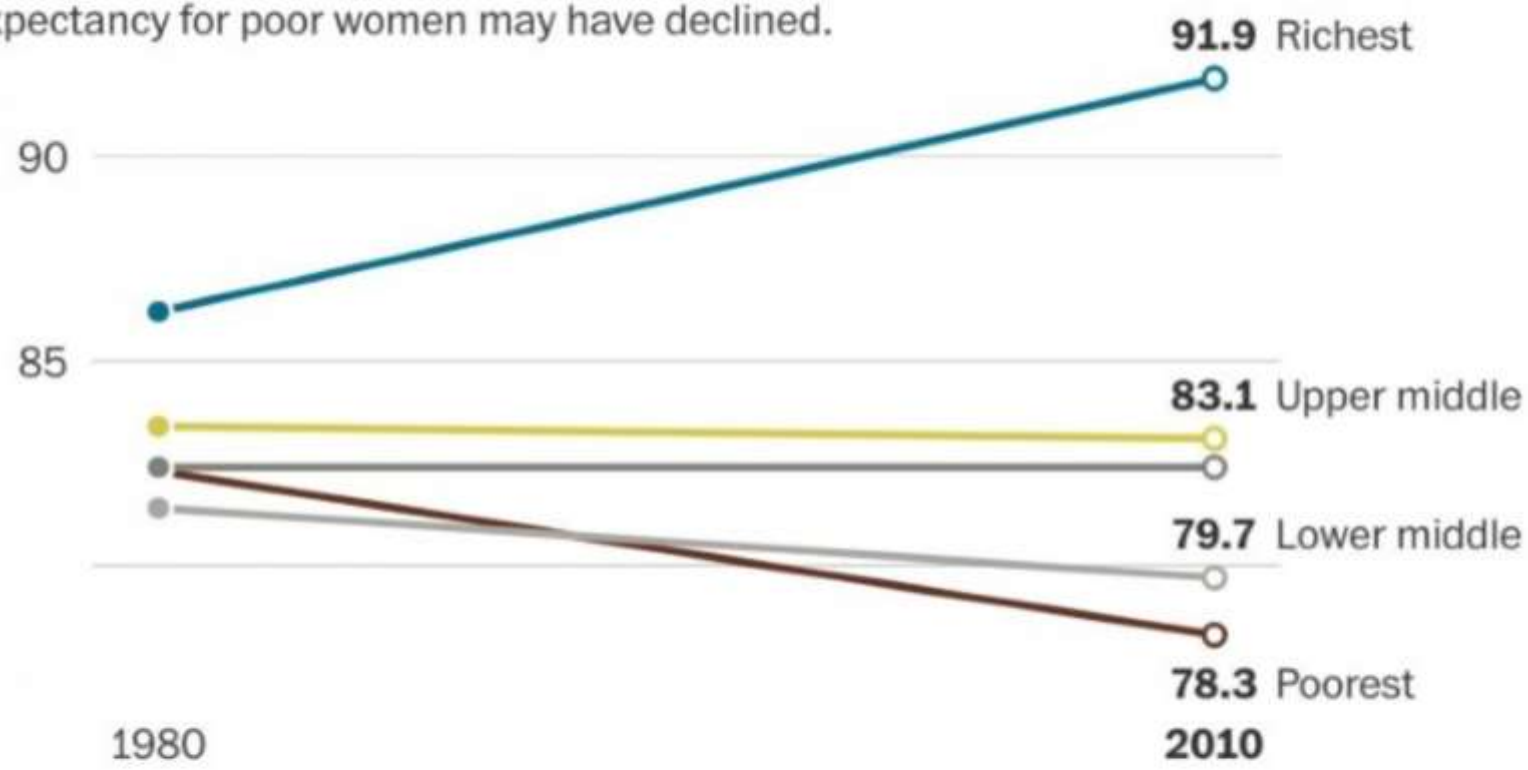
NOTES: Red circles depict newborn life expectancy in the United States. Grey circles depict life expectancy values for Australia, Austria, Belgium, Canada, Denmark, Finland, France, Iceland, Ireland, Italy, Japan, Luxembourg, the Netherlands, New Zealand, Norway, Portugal, Spain, Sweden, Switzerland, the United Kingdom, and West Germany.

SOURCE: National Research Council (2011, Figure 1-4).

US Health in International Perspective. Shorter lives, poorer health. S Woolf, L Aron, eds. NRC and IOM. 2012.

Inequality in life expectancy widens for women

Wealthier women can expect to live longer than their parents did, while life expectancy for poor women may have declined.

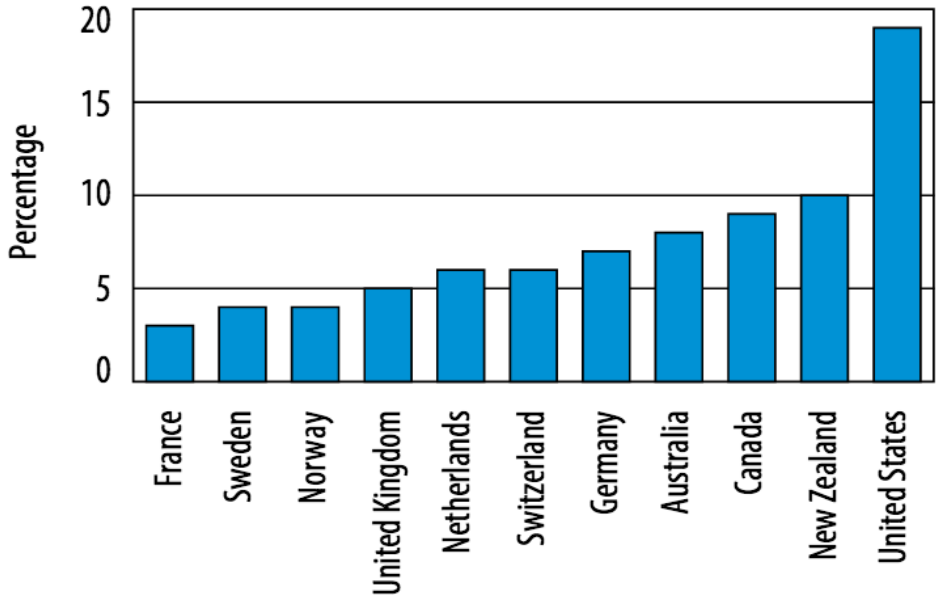


Life expectancy for 50-year-olds in a given year, by quintile of income over the previous 10 years

Source: National Academies of Science, Engineering and Medicine

National Academy of Medicine. The growing gap in life expectancy by income: Implications for federal programs and policy responses. 2015. http://www.nap.edu/download.php?record_id=19015#

Fig. 4.3. **Percentage of adults aged 65 years or older who had problems accessing health-care services during the past year due to their cost, 11 countries, 2014**

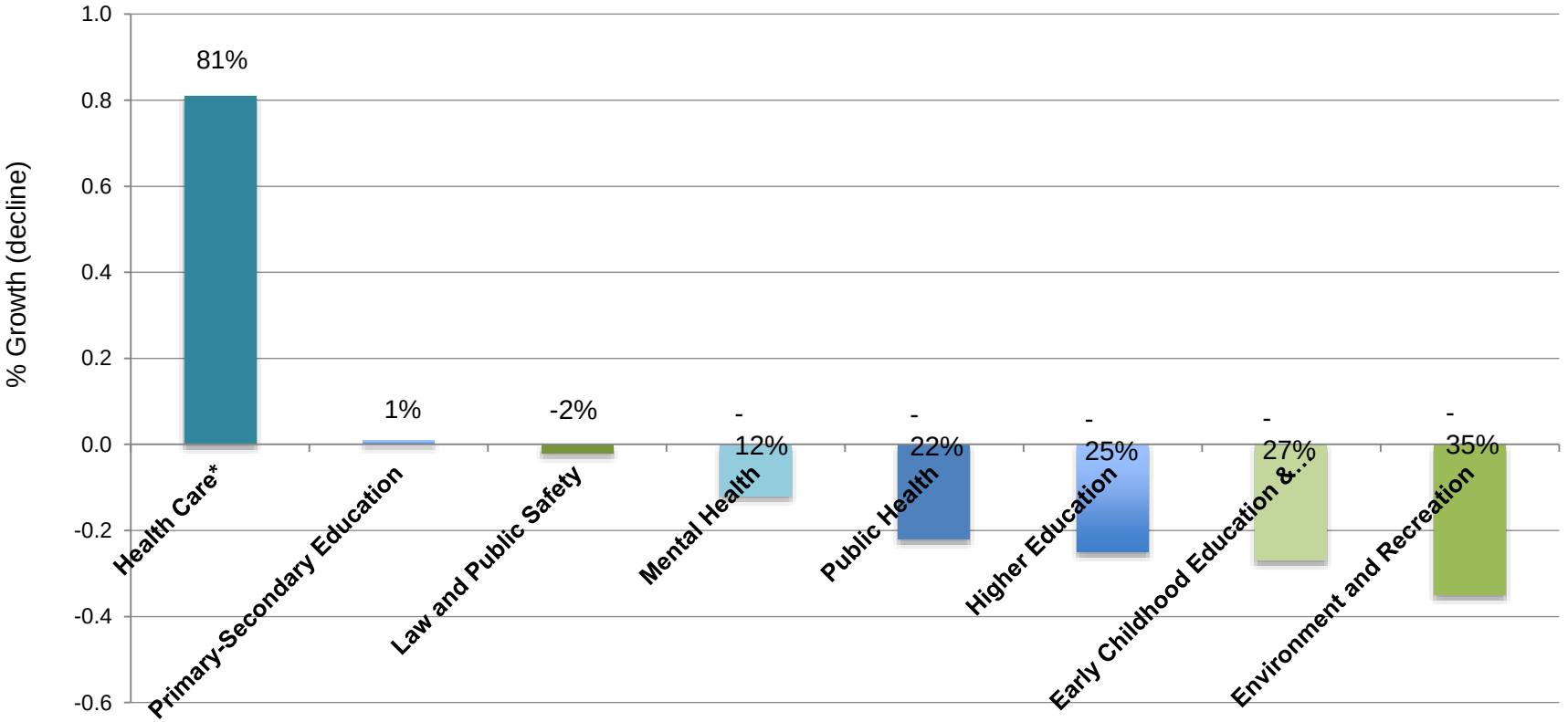


Note: Because of the cost, respondents with a medical problem did not visit a doctor, missed a medical test or treatment recommended by a doctor, did not fill out a prescription or missed a dose of medicine, or a combination of these.
Source: (*6*).

World Health Organization, "World Report on Ageing and Health."
<http://apps.who.int/iris/bitstream/10665/186463/1/9789240694811_eng.pdf?ua=1> Accessed March 25, 2016

2. Resource allocation, investing in the future

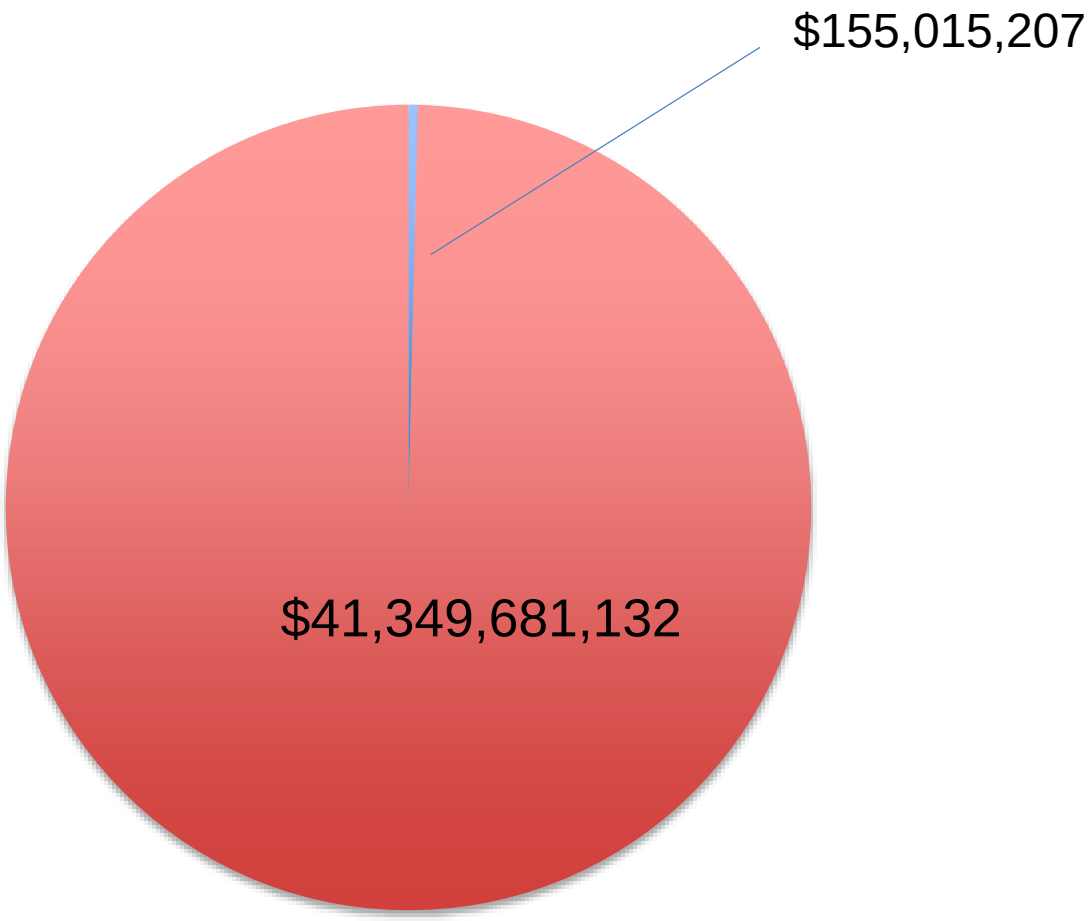
Change in Massachusetts State Government spending: 2001-14



* Health care expenditure is Group Insurance Commission spending plus MassHealth (Medicaid)

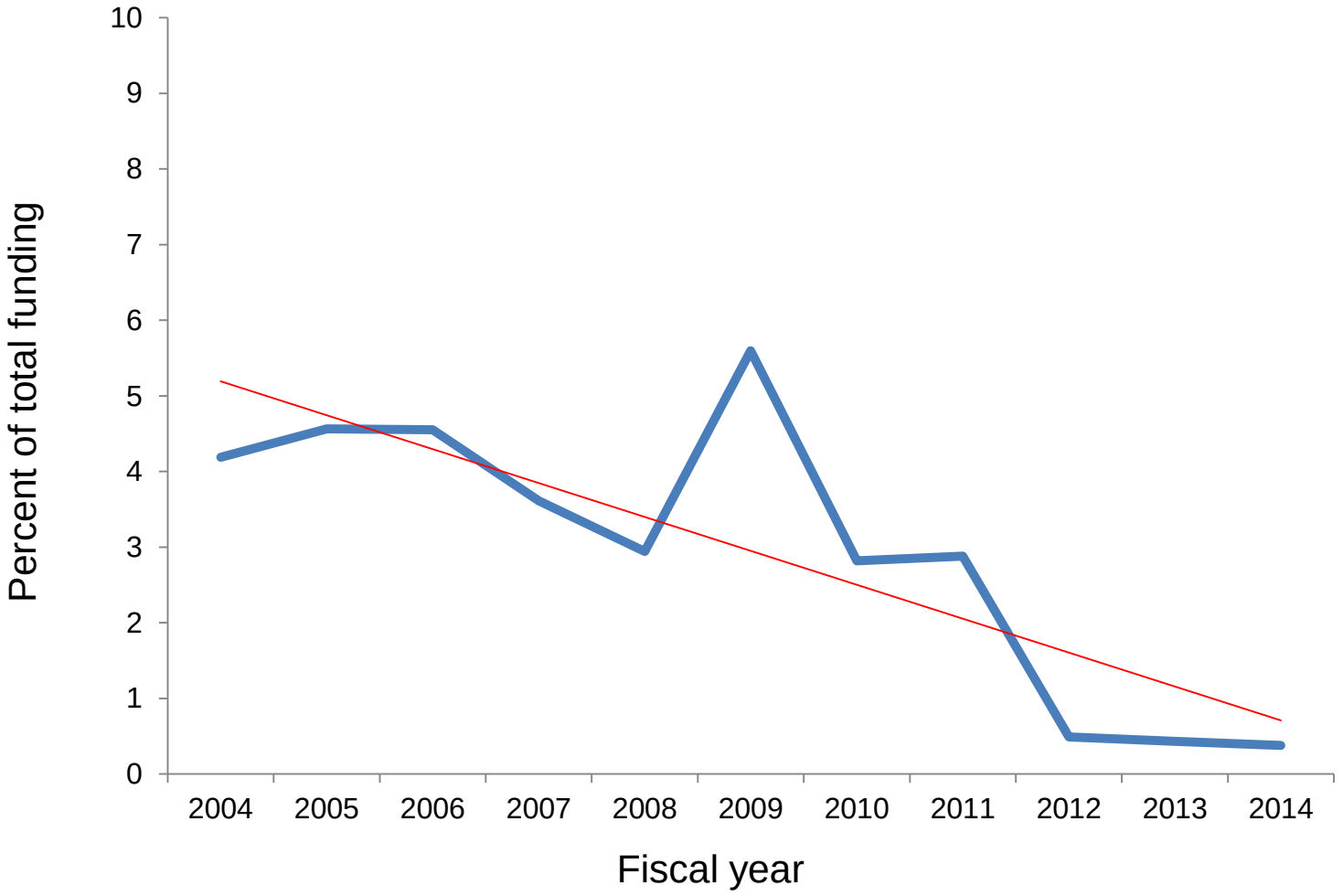
"Healthy People/Healthy Economy: An Initiative to Make Massachusetts the National Leader in Health and Wellness." 2015. Data from Massachusetts Budget and Policy Center Budget Browser. <http://www.tbf.org/tbf/56/hphe/Health-Crisis>

Among NIH funding for the current fiscal year, only 0.4% was awarded to projects with the terms “population” or “public” in the title



NIH RePORTER. Current projects from FY 2013-2014 for which funding data is available. <http://projectreporter.nih.gov/reporter_ChartResults.cfm?icde=22550343> Accessed on November 19, 2014.

Proportion of NIH funding awarded to projects with the terms “population” or “public” in the title, abstract, or terms

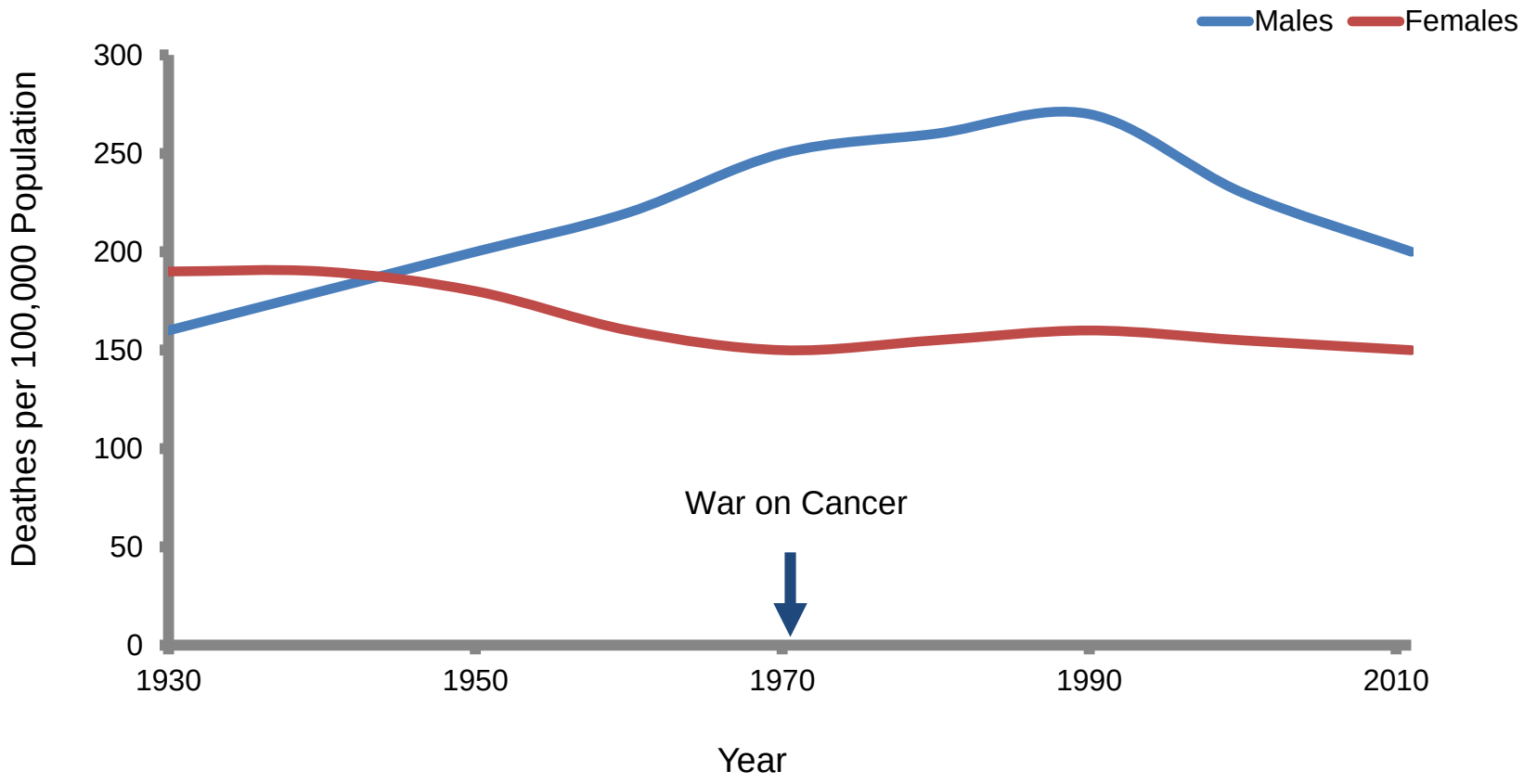


NIH RePORTER. Search results for projects for which funding data is available. <http://projectreporter.nih.gov/reporter.cfm> Accessed on November 20, 2014.

3. Hype over hope

“The time has come in America when the same kind of concentrated effort that split the atom and took man to the moon should be turned toward conquering this dread disease. Let us make a total national commitment to achieve this goal.”

President Richard Nixon, signing into law the National Cancer Act of 1971, December 1970



Siegel et al. Cancer statistics, 2014. CA Cancer J Clin (2014)

Slide courtesy of Michael Joyner

“Last year, Vice President Biden said that with a new moonshot, America can cure cancer . . . .Let’s make America the country that cures cancer once and for all.”

President Barak Obama, State of the Union address, January 2016

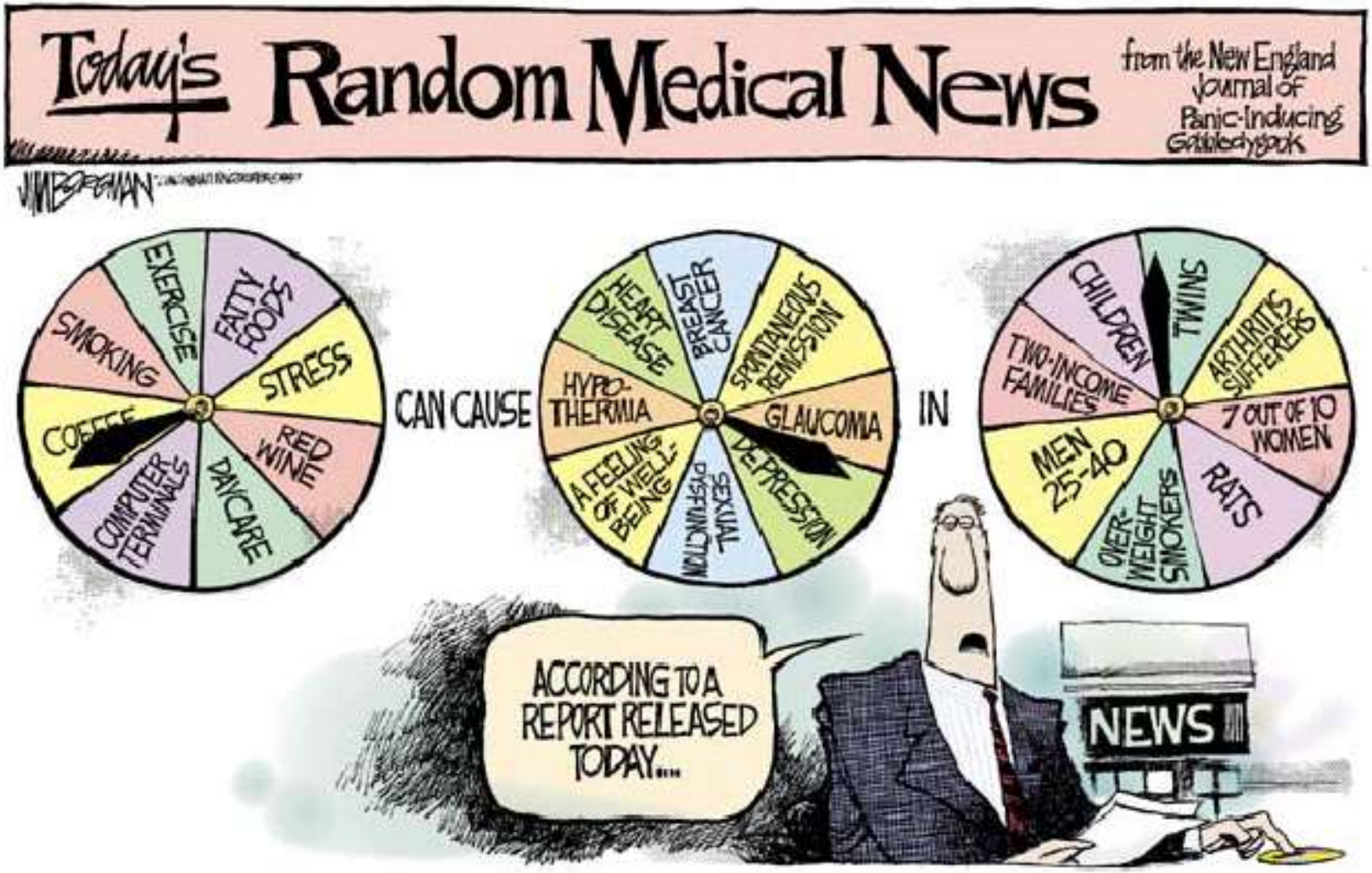
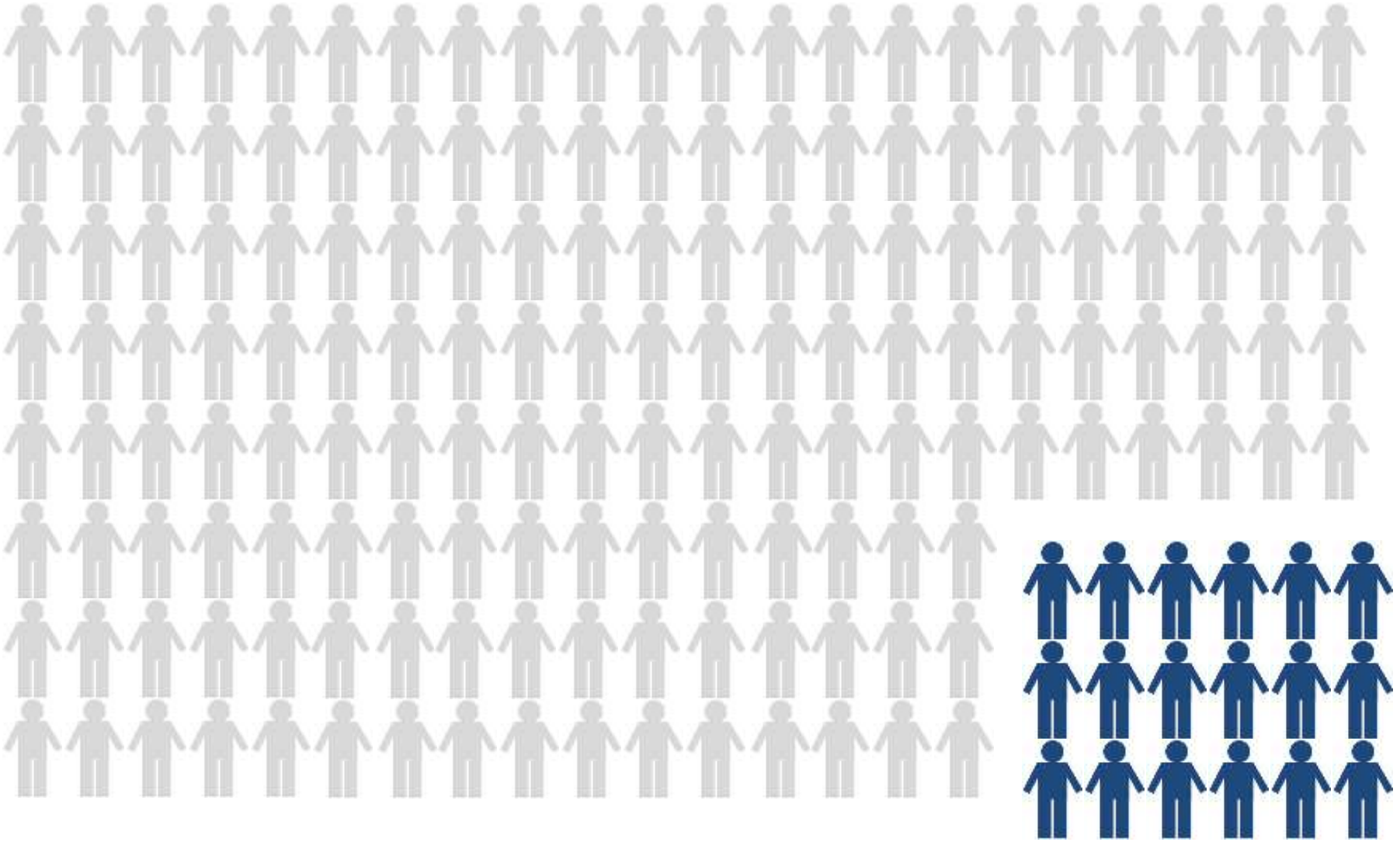
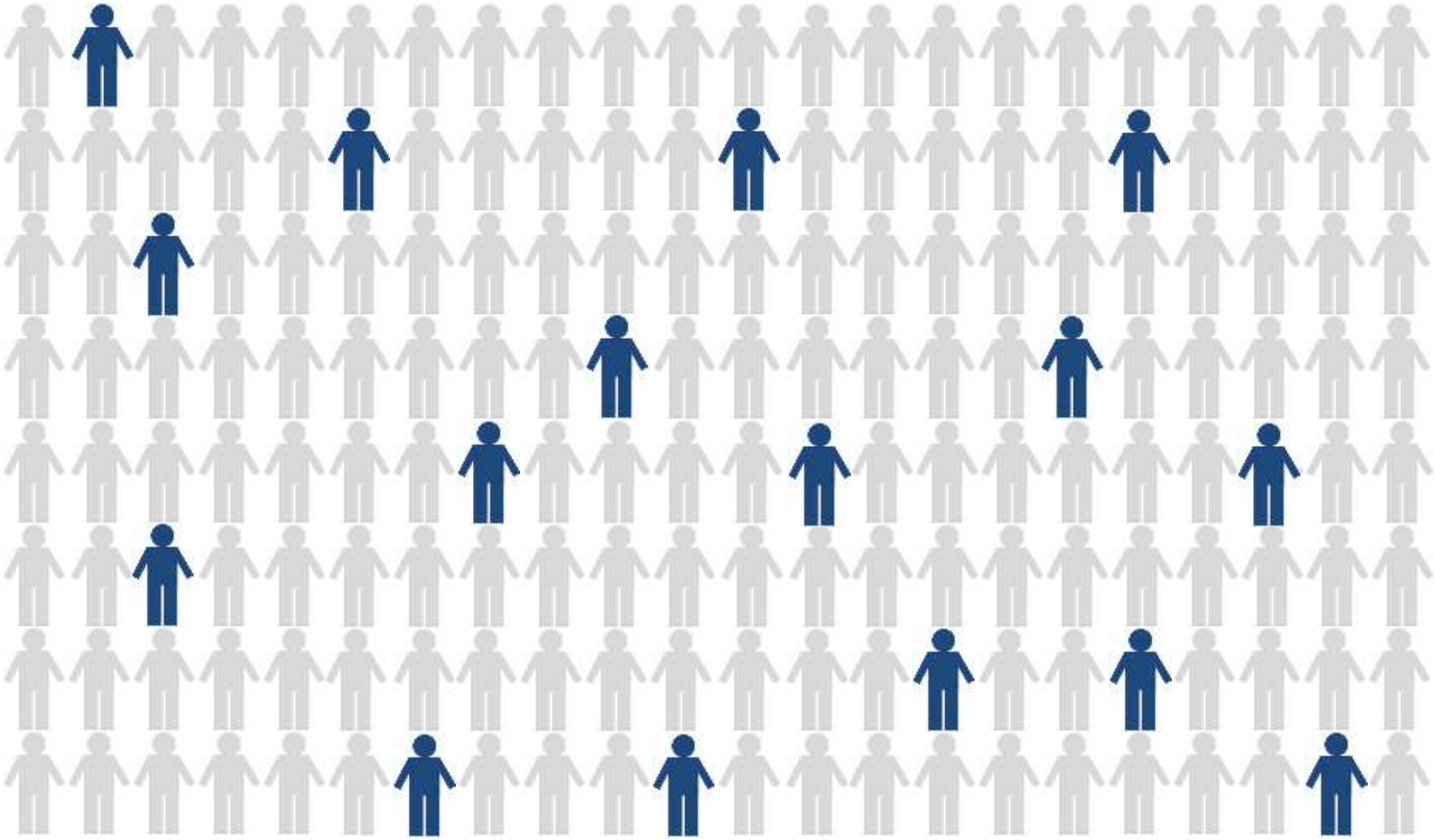


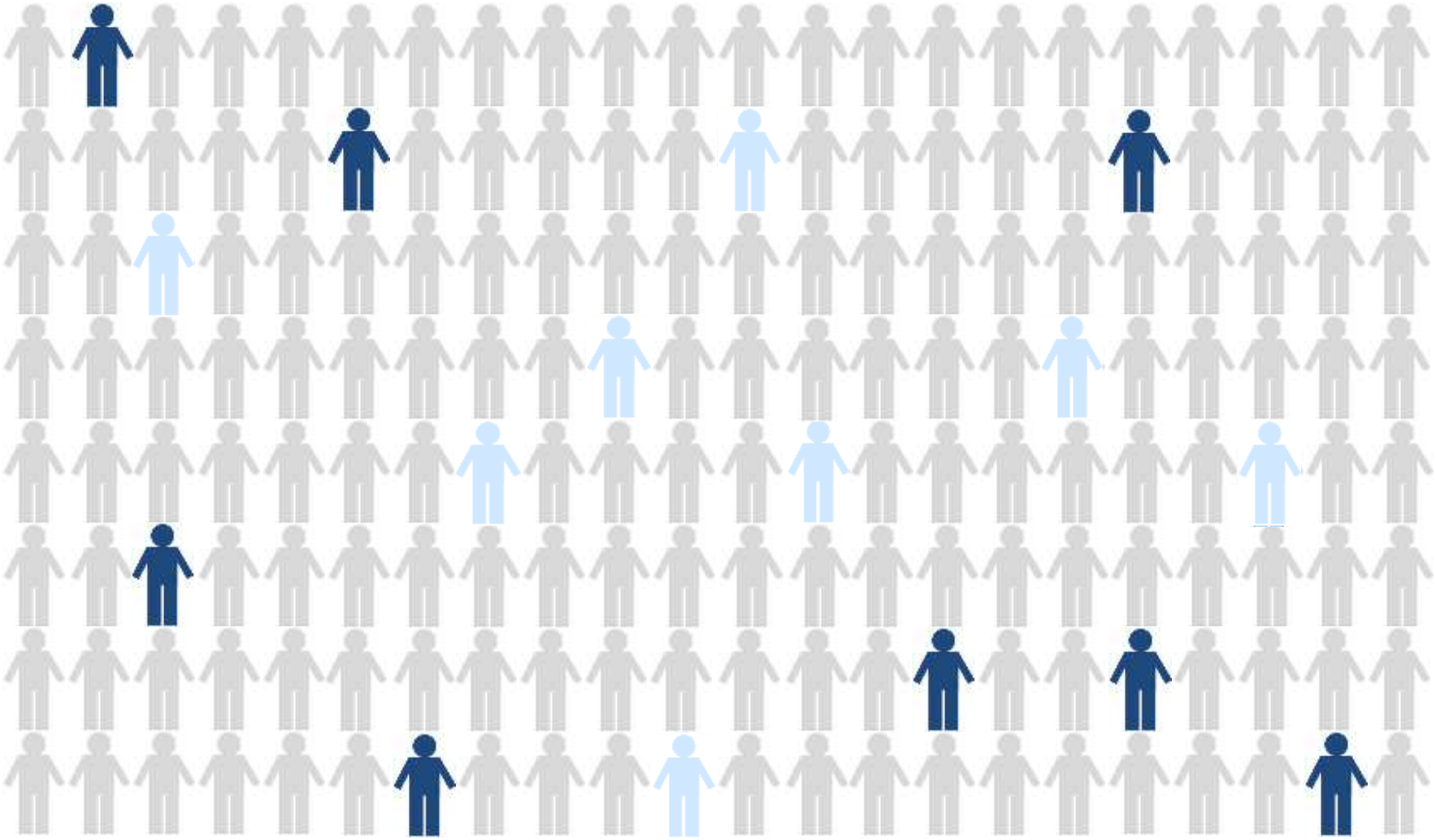
Figure 3: New England Journal of Panic-Inducing Gobbledygook.
Source: Jim Borgman, The Cincinnati Enquirer (27 April 1997, E4).

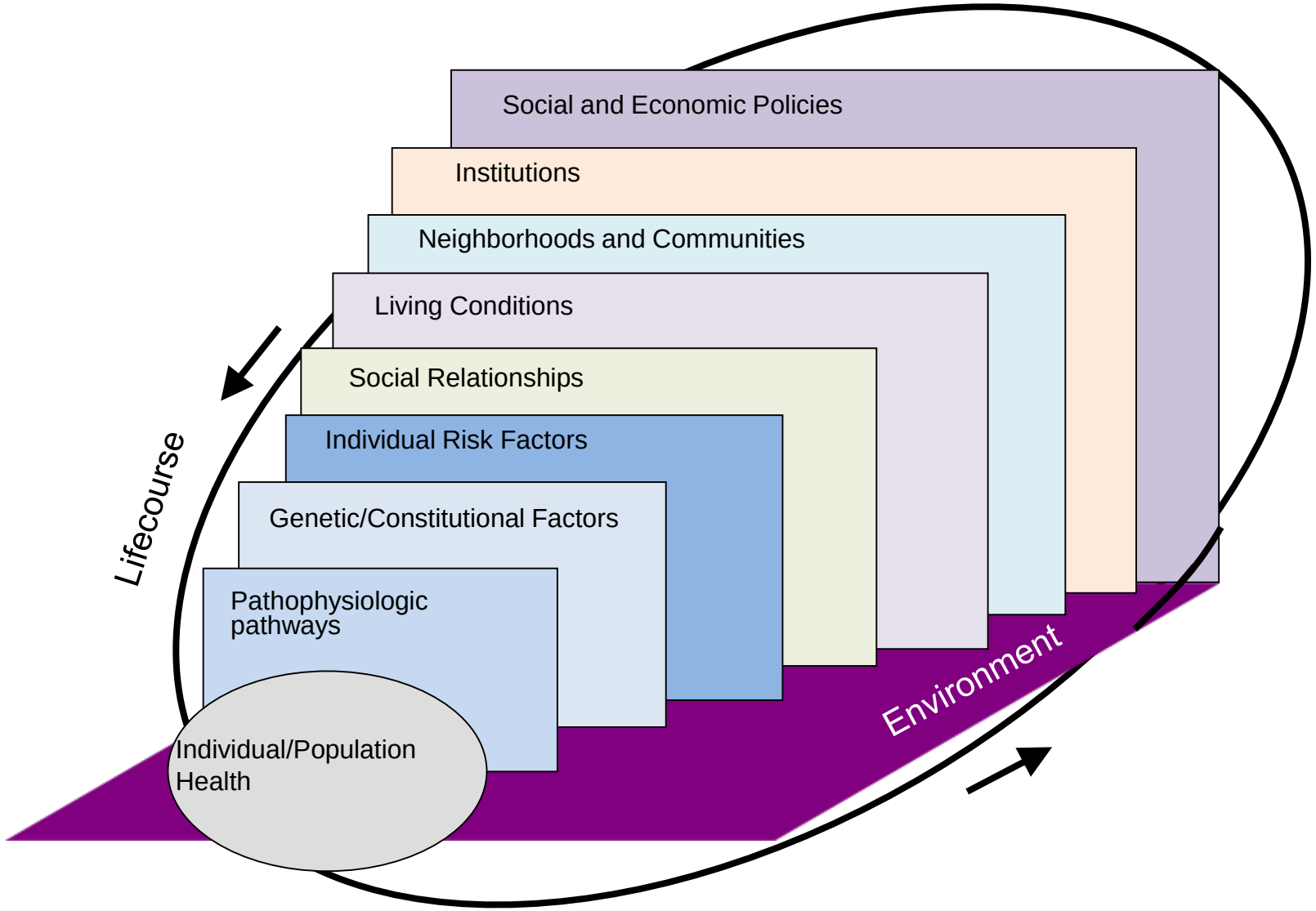
Unless.

http://graphics8.nytimes.com/images/2009/03/11/opinion/13population.480.jpg









Kaplan, G. What's wrong with social epidemiology, and how can we make it better? *Epid Rev* 2004; 26: 124-135

VIEWPOINT

Will Precision Medicine Improve Population Health?

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Announcement of the precision medicine initiative has led to a variety of responses, ranging from enthusiastic expectations[1] to explicit skepticism,[2] about potential health benefits, limitations, and return on investment. This Viewpoint discusses whether precision medicine is unlikely or likely to improve population health, aiming to forge a consensus that bridges disparate perspectives on the issue. The potential of precision medicine to improve the health of individuals or small groups of individuals is not addressed here because it involves a different question with different metrics.

Precision Medicine Is Unlikely to Improve Population Health

There are 3 fundamental reasons why precision medicine might not improve the health of populations. First, disease pathogenesis, especially for common noncommunicable diseases, is extraordinarily complex. Abundant evidence has demonstrated this for the association between the multiplicity of specific genes and conditions, including obesity, hypertension, or certain cancers. Additionally, it is known that genetic associations have, in most instances, small effect sizes in contrast with more robust contributions of behavioral and social factors.

Second, a central promise of precision medicine is the identification of predictors of disease that can help guide interventions. This may prove to be the case for some diseases, especially cancer, but is unlikely to be the case for most other complex diseases. The challenge arises from the mathematical foundations of genetic epidemiology. Although large population studies can identify associations between genotypes and phenotypes, resulting associations have limited capacity to predict phenotype in individuals, which is the ultimate goal of precision medicine. It would take substantially stronger associations—several orders of magnitude greater than have been identified so far—to provide sufficient evidence to improve disease prediction in individuals.

Third, an assumed potential benefit of precision medicine (predicated on accurate and meaningful risk prediction) is that disease in the population can be avoided or forestalled by large numbers of individuals who, when provided with accurate risk prediction, will change their behavior to mitigate their personal risk. Although this may seem intuitively plausible, current data suggest that individuals do not change their behavior much even when they become aware of being in a high-risk group.[3]

Overemphasis on precision medicine by the scientific community and health systems could pose a challenge to the health of populations for other reasons. First, the United States faces extraordinary challenges to the health of its population. Over the past 30 years, the United States has fallen behind other high-income peer nations in health attainment on many metrics, including life expectancy and infant mortality, and there are persistent gaps in health outcomes by income and race/ethnicity.[4] The solution to these challenges is probably not an increased focus on the individual, but rather involves focusing on the social, economic, and structural drivers of population health that are ubiquitous and inevitably linked to health achievement as a country. The centrality of the precision medicine effort to the US national health research agenda may distract from efforts to remedy the foundational causes of ill health such as poverty, obesity, and education. Without addressing these causes, there will be little, if any, success in reversing the trends of poor achievement in US population health.

Second, precision medicine could (and to some extent has) led to a shift from which projects are funded by health research agencies. Funding for grants with a population health or public health goal has declined over the past 10 years at the National Institutes of Health, whereas funding for *-omic* research has increased substantially. This shift in funding may lead to an emerging generation of health scientists who see the world through an individualist lens and may not engage in factors that can improve the health of populations.

Third, the promise of precision medicine may lead to other promises such as the recently announced cancer "moonshot," which may echo previous efforts that have not lived up to expectations. The hype, which could become unrealized health benefits, could lead to disillusionment in the goals of health science, with potential lasting consequences affecting public confidence and investment in medical research.

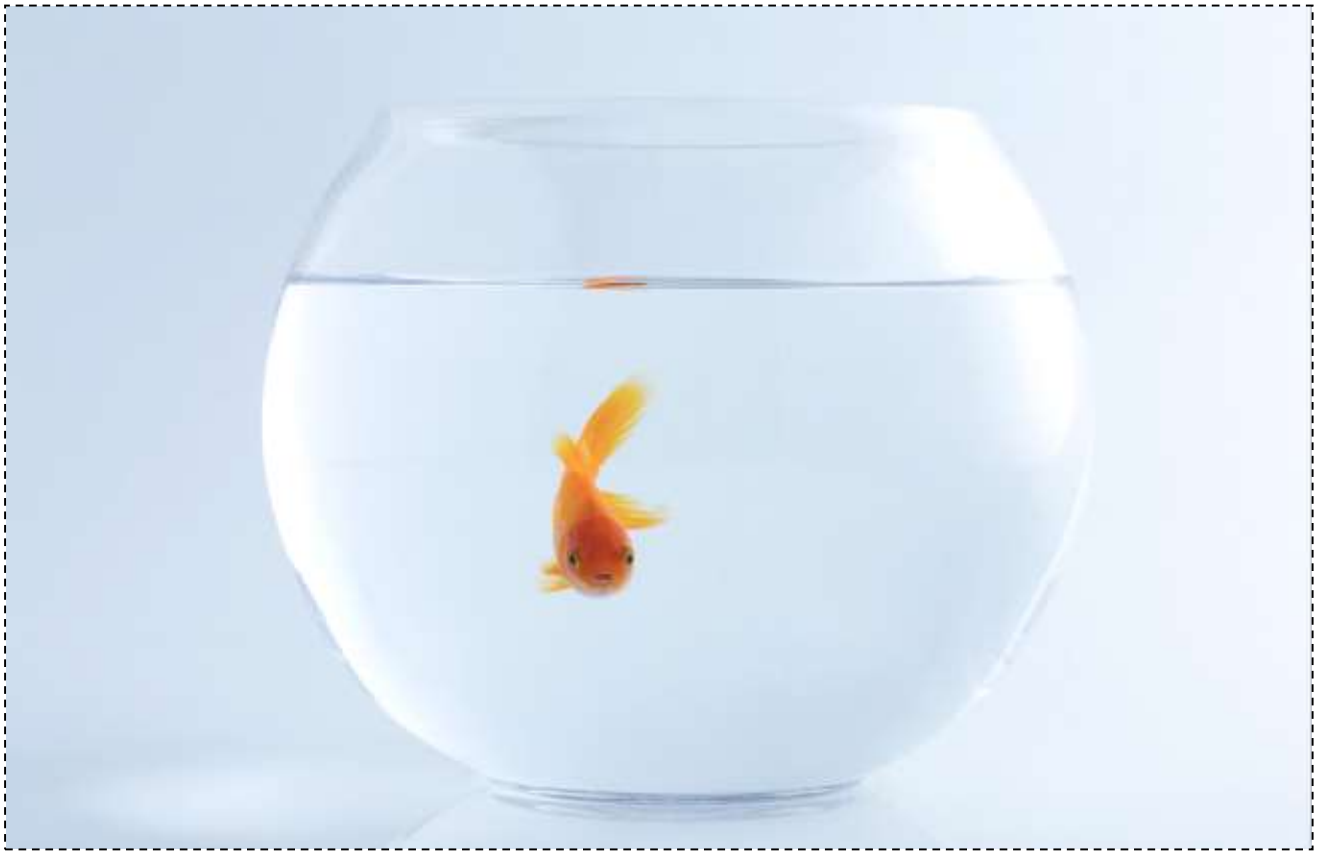
Precision Medicine Can Improve Population Health

By contrast, there are 3 fundamental reasons that advances in precision medicine might improve population health. First, population health could improve by applying complementary individual and public health approaches to health care and disease prevention. A focus on the wider environmental and social determinants of health is of great importance in addressing health inequities. However, pitting the health of individuals against the health of populations risks widening an unnecessary divide between medicine and public health. Population health planning requires directing efficient use of resources toward those most at risk. Stratification of populations into risk groups for multiple chronic diseases could provide more efficient and effective prevention and treatment strategies and

“I know this is a formidable technical task, one that may not be accomplished before the end of this century. Yet, current technology has attained a level of sophistication where it is reasonable for us to begin this effort. It will take years, probably decades, of effort on many fronts. There will be failures and setbacks just as there will be successes and breakthroughs. And as we proceed we must remain constant ….but isn't it worth every investment necessary….We know it is! ”

President Ronald Reagan announcing the launch of Star Wars, 1980.

"My loyal opposition wasn't loyal enough."



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