BIOTECH 201

How can Biotech...?

Week 3 - February 27, 2018

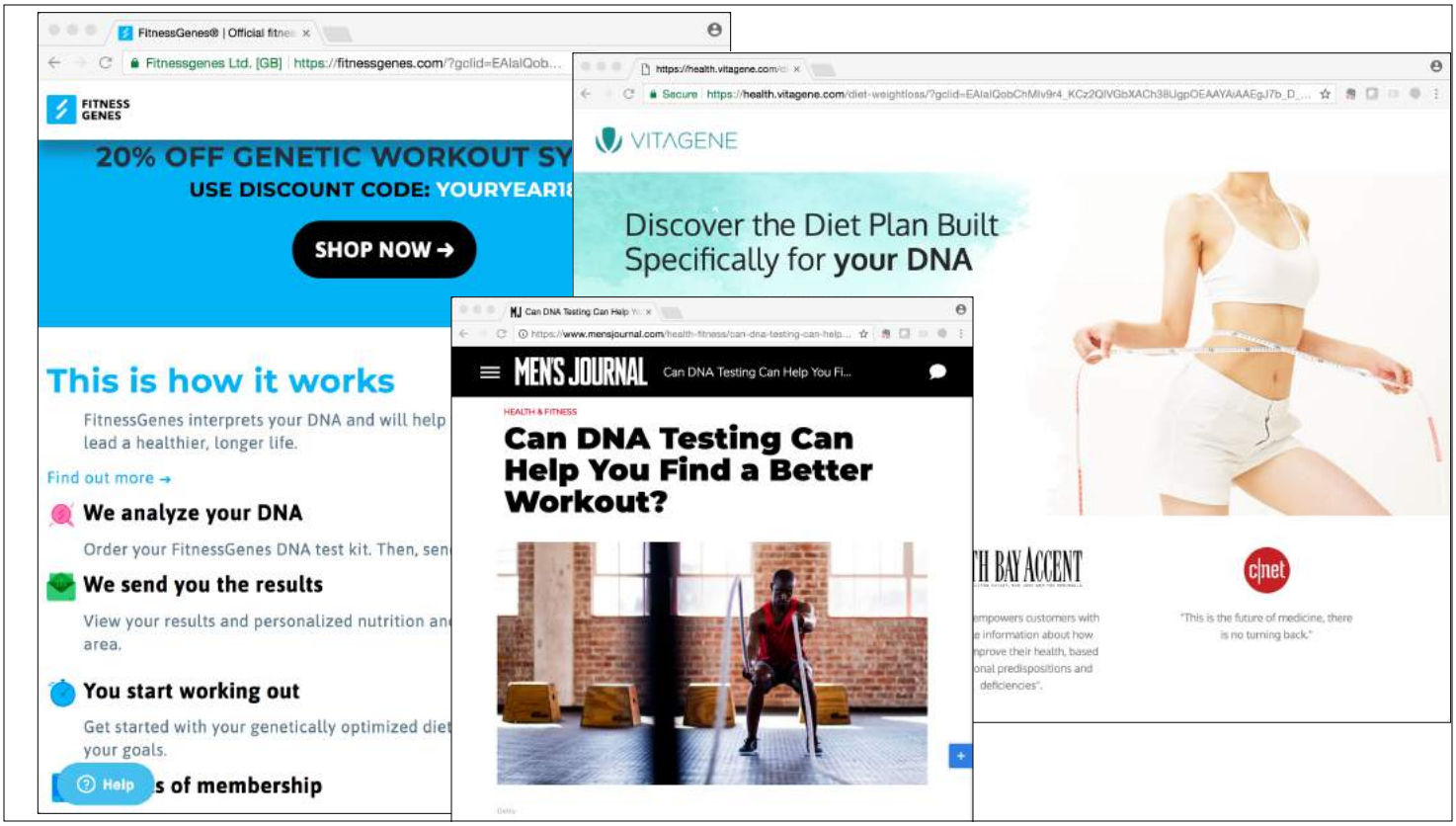
HUDSONALPHA INSTITUTE FOR BIOTECHNOLOGY

Tonight's topics

Feb 13	solve a crime? store information in DNA?
Feb 20	change my DNA? create "designer babies"?
Feb 27	help me lose weight? predict my death?
March 6	help us reach and colonize Mars?

How can Biotech...

help me lose weight?



Two ways gene-trait studies occur

hypothesis-dependent

based on prior evidence; may be suggestive of cause-effect

hypothesis-independent

requires no prior knowledge, studies a broad set of potential options and looks for statistically significant associations

2007 Stanford Study

311 overweight post-menopausal women assigned to a particular diet for one year

		avg weight loss (lbs)
very low-carb	**Atkins**	**10.4**
40% carb, 30% protein, 30% fat	**Zone**	**3.5**
behavior change	**LEARN**	**5.7**
very low-fat	**Ornish**	**4.9**

within each diet group, there was a 40-50 lb range of loss/gain

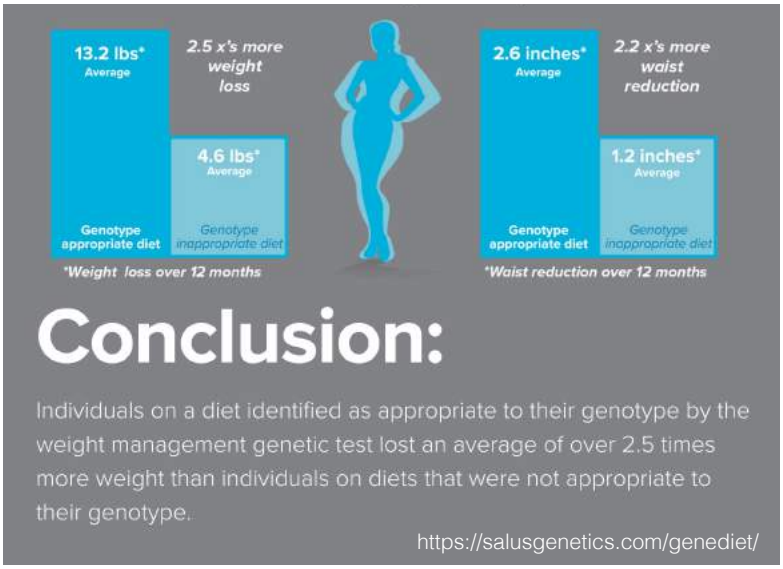
Gardner C. et al. Comparison of the Atkins, Zone, Ornish, and LEARN diets for change in weight and related risk factors among overweight premenopausal women: the A TO Z Weight Loss Study: a randomized trial. JAMA. 2007 Mar 7;297(9):969-77.

2010 Stanford Follow-On Study

analyzed DNA markers in 3 genes (PPARG, ADRB2, FABP2) for 133 women from the original study

identified specific genetic combinations that suggested

- low carb responsive
- low fat responsive
- balanced diet responsive



Nelson MD et al. Genetic Phenotypes Predict Weight Loss Success: The Right Diet Does Matter. (Oral Presentation #4). Presented at the American Heart Association's Joint Conference – 50th Cardiovascular Disease Epidemiology and Prevention and Nutrition, Physical Activity and Metabolism – 2010, March 2-5, 2010, San Francisco, CA.

What are these genes?

PPARG - peroxisome proliferator-activated receptor gamma
The product of this gene regulates other genes implicated in **insulin signaling, lipid storage, fatty acid uptake, and glucose uptake**. The DNA variant of interest was first identified in 1997 and seems to alter how well the PPARG protein can carry out its regulatory duties

ADRB2 - adrenergic-receptor beta2
This gene produces a protein that binds the neurotransmitter epinephrine and initiates a set of signals inside cells communicate information within the cell. Among other things, it **helps regulate insulin secretion from the pancreas and stimulates the release and use of fatty acids from fat cells**.

FABP2 - fatty acid binding protein 2
The protein encoded by this gene binds and helps breakdown certain types of fatty acids. The DNA variant **alters fat breakdown and appears to impair the removal of sugar from the bloodstream**.

2018 Stanford Replication Study

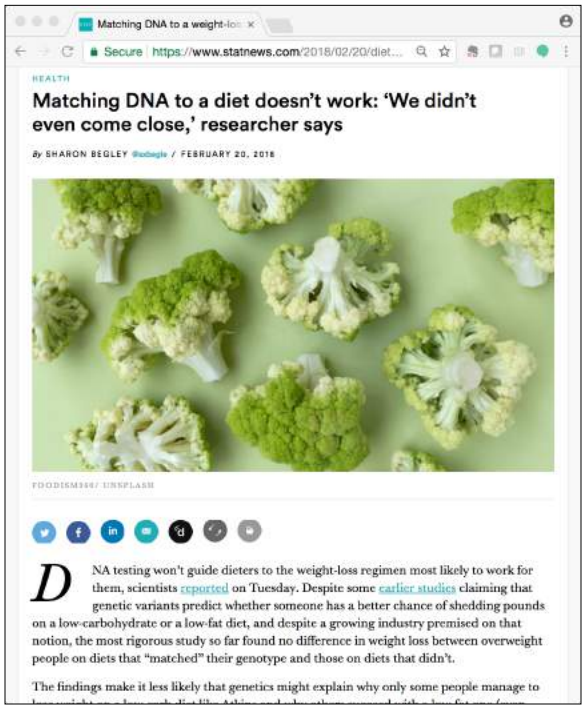
609 overweight adults, randomized to 1 year of low-fat or low-carb diet
all tested at the 3 gene regions

79% completed trial

avg weight loss:
11.7 lbs for low fat
13.2 lbs for low carb

No significant interaction between DNA results and diet-plan success

Gardner C., et al. Effect of Low-Fat vs. Low-Carbohydrate Diet on 12 Month Weight Loss in Overweight Adults and the Association with Genotype Pattern or Insulin Secretion: The DIETFITS Randomized Clinical Trial. JAMA 2018;319(7):667–679



Matching DNA to a weight-loss

Secure | https://www.statnews.com/2018/02/20/diet...

HEALTH

Matching DNA to a diet doesn't work: 'We didn't even come close,' researcher says

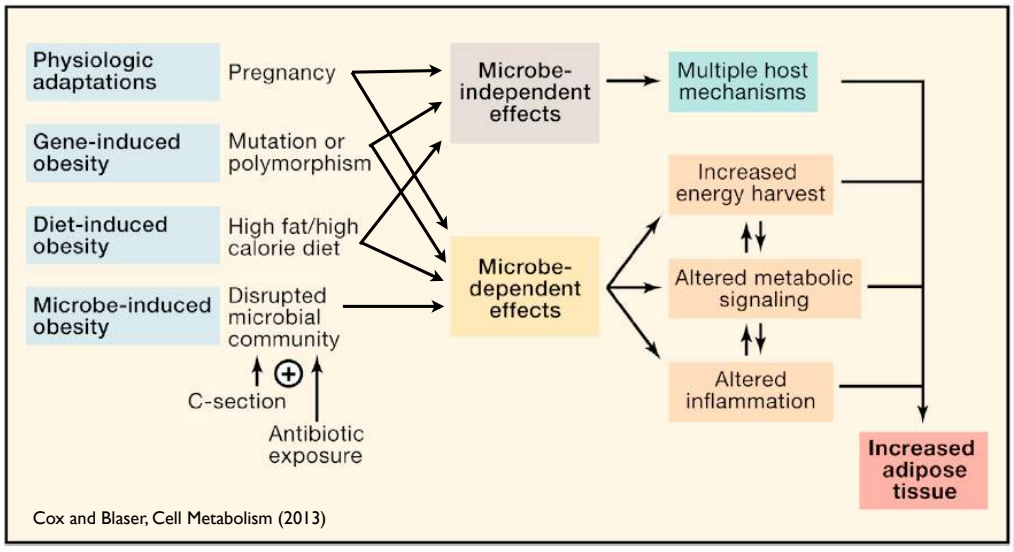
By SHARON BEGLEY / FEBRUARY 20, 2018

DNA testing won't guide dieters to the weight-loss regimen most likely to work for them, scientists reported on Tuesday. Despite some earlier studies claiming that genetic variants predict whether someone has a better chance of shedding pounds on a low-carbohydrate or a low-fat diet, and despite a growing industry premised on that notion, the most rigorous study so far found no difference in weight loss between overweight people on diets that "matched" their genotype and those on diets that didn't.

The findings make it less likely that genetics might explain why only some people manage to

So… is there a role for genetics?

Genetic influences on energy metabolism and weight are very likely… but probably more complex than a three-gene combination.



Cox and Blaser, Cell Metabolism (2013)

Other researchers are looking at combinations of hundreds or thousands of genetic variants…this requires large numbers of participants and replication of any findings

DNA impact on exercise or nutrient intake?

Consensus statement — British Journal of Sports Medicine 2015

OPEN ACCESS

Direct-to-consumer genetic testing for predicting sports performance and talent identification: Consensus statement

Nick Webborn,[1] Alun Williams,[2] Mike McNamee,[3] Claude Bouchard,[4] Yannis Pitsiladis,[5] Ildus Ahmetov,[6] Euan Ashley,[7] Nuala Byrne,[8] Silvia Camporesi,[9] Malcolm Collins,[10] Paul Dijkstra,[11] Nir Eynon,[12] Noriyuki Fuku,[13] Fleur C Garton,[14] Nils Hoppe,[15] Søren Holm,[16] Jane Kaye,[17] Vassilis Klissouras,[18] Alejandro Lucia,[19] Kamiel Maase,[20] Colin Moran,[21] Kathryn N North,[14] Fabio Pigozzi,[22] Guan Wang[5]

▸ Additional material is published online only. To view please visit the journal online (http://dx.doi.org/10.1136/bjsports-2015-095343).

For numbered affiliations see end of article.

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ABSTRACT
The general consensus among sport and exercise genetics researchers is that genetic tests have no role to play in talent identification or the individualised

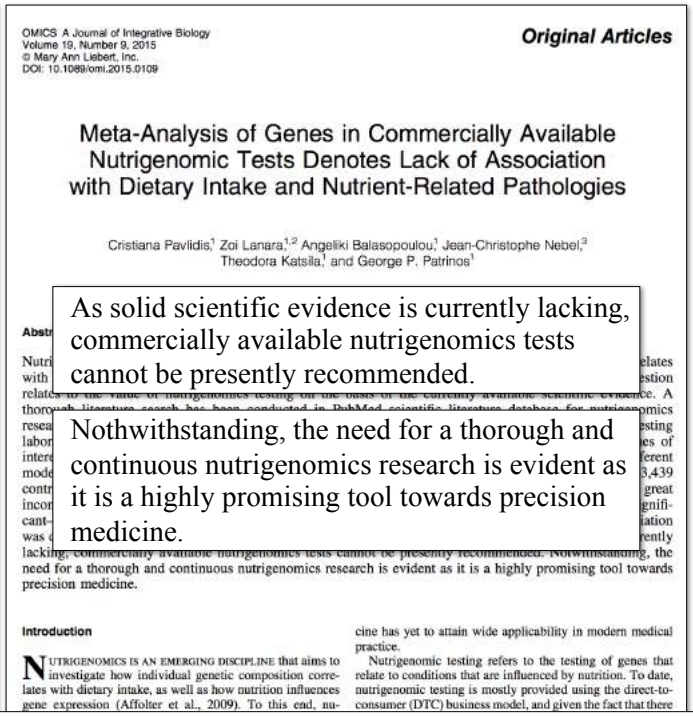
The general consensus among sport and exercise genetics researchers is that genetic tests have no role to play in talent identification or the individualised prescription of training to maximise performance.

of the evidence in relation to genetic testing and the limitations of current knowledge. This article reviews the issues around the currently available evidence behind the genetic testing, comments on

Consequently, in the current state of knowledge, no child or young athlete should be exposed to DTC genetic testing to define or alter training or for talent identification aimed at selecting gifted children or adolescents.

current state of knowledge, no child or young athlete should be exposed to DTC genetic testing to define or alter training or for talent identification aimed at selecting gifted children or adolescents. Large scale collaborative projects, may help to develop a stronger scientific foundation on these issues in the future.

for DTC Genetic Testing in relation to screening for disease, or to identifying genetic carriers, including those from the European Workshop on Genetic Testing Offer in Europe, the Human Genetics Commission (UK), American College of Medicine Genetics among others.[1–3] However,



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Original Articles

Meta-Analysis of Genes in Commercially Available Nutrigenomic Tests Denotes Lack of Association with Dietary Intake and Nutrient-Related Pathologies

Cristiana Pavlidis,[1] Zoi Lanara,[1,2] Angeliki Balasopoulou,[1] Jean-Christophe Nebel,[3] Theodora Katsila,[1] and George P. Patrinos[1]

As solid scientific evidence is currently lacking, commercially available nutrigenomics tests cannot be presently recommended.

Nothwithstanding, the need for a thorough and continuous nutrigenomics research is evident as it is a highly promising tool towards precision medicine.

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Introduction

NUTRIGENOMICS IS AN EMERGING DISCIPLINE that aims to investigate how individual genetic composition correlates with dietary intake, as well as how nutrition influences gene expression (Affolter et al., 2009). To this end, nu-

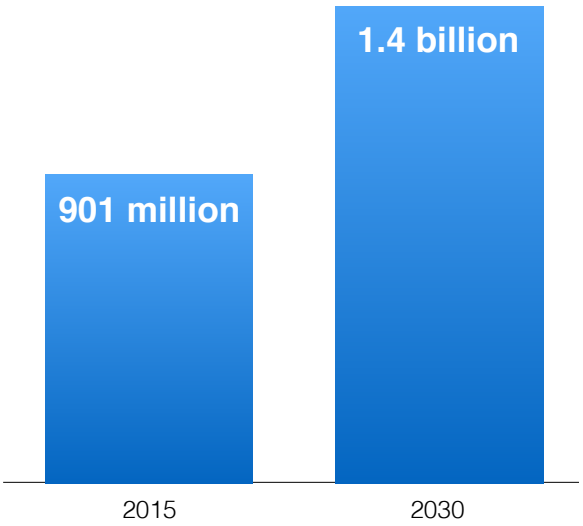
cine has yet to attain wide applicability in modern medical practice.

Nutrigenomic testing refers to the testing of genes that relate to conditions that are influenced by nutrition. To date, nutrigenomic testing is mostly provided using the direct-to-consumer (DTC) business model, and given the fact that there

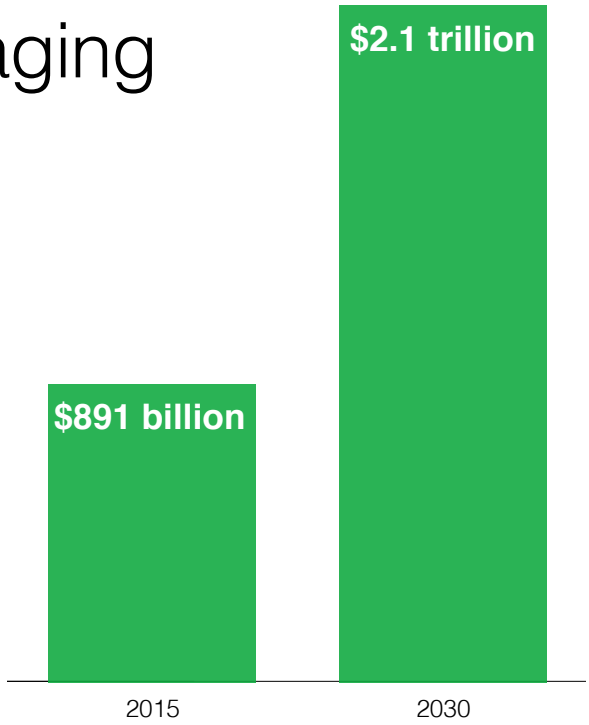
How can Biotech...

predict my ~~death?~~ *biological age?*

The challenge of aging



global # of people 60+ years old



global costs for dementia

Finding interventions that slow aging

Waiting 10-20 years to determine if an intervention successfully slows aging is challenging.

1. Develop a biomarker of biological age

helps determine individual health status and aging disease risk

2. Find interventions that affect the biomarker

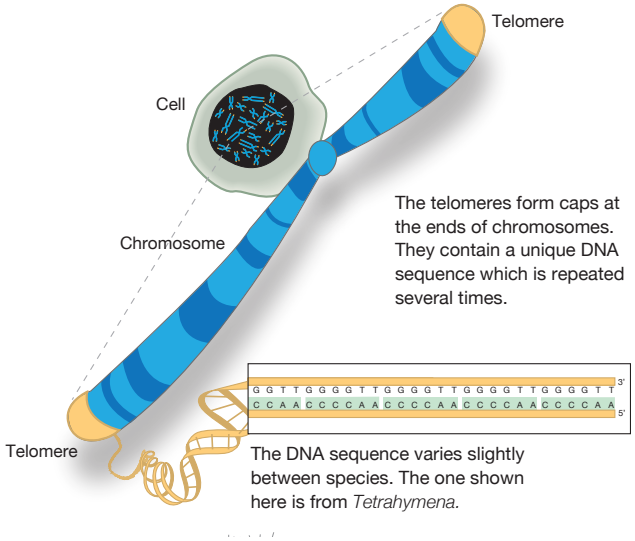
gene editing, drug screening, etc.
test in cells, then model organisms

3. Conduct clinical trials of intervention

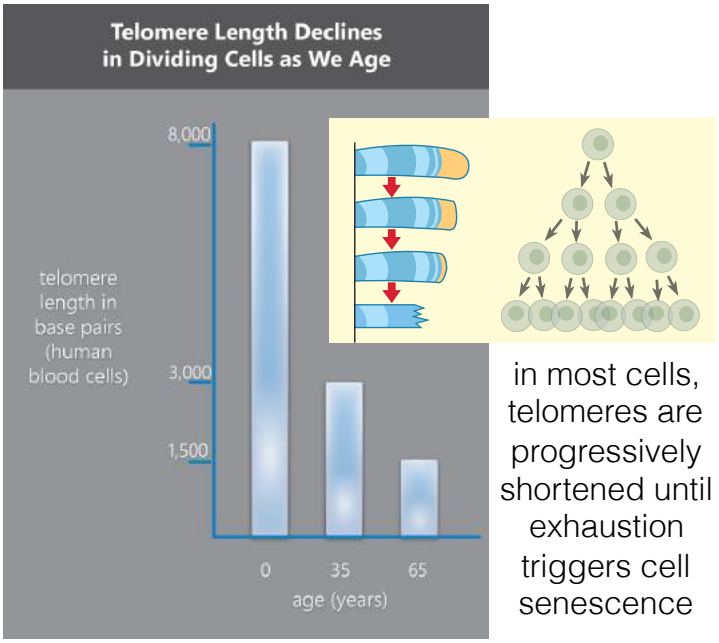
use the biomarker as a proxy for age - does the intervention slow aging?

Current candidate aging biomarkers

Telomere Length



www.nobelprize.org

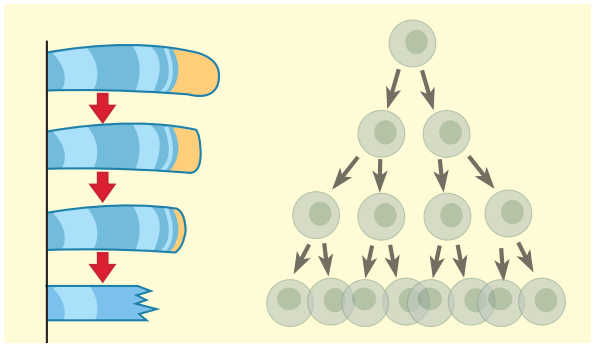


in most cells, telomeres are progressively shortened until exhaustion triggers cell senescence

http://learn.genetics.utah.edu/content/basics/telomeres/

Current candidate aging biomarkers

Telomere Length



> 6,000 papers published on "telomere length"

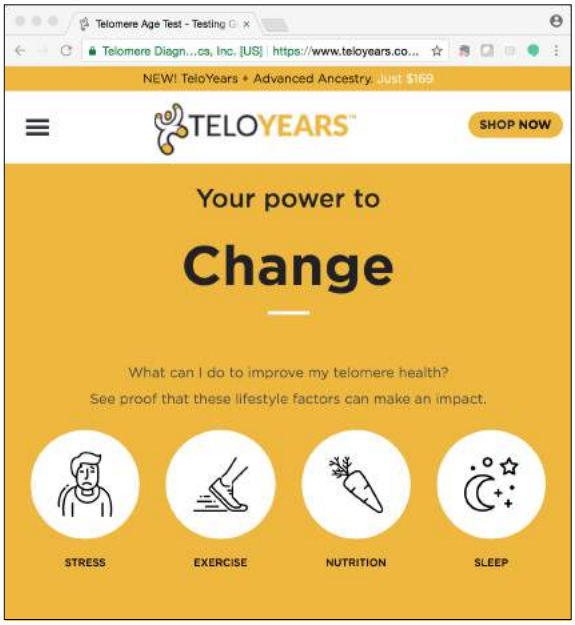
women have on avg. longer telomeres than men

short telomeres associated with increased mortality risk, coronary heart disease, Alzheimer and other measures of age-related traits (cognition, physical function)

very long telomeres linked to greater risk of melanoma, lung cancer, some types of leukemia and brain tumors

Current candidate aging biomarkers

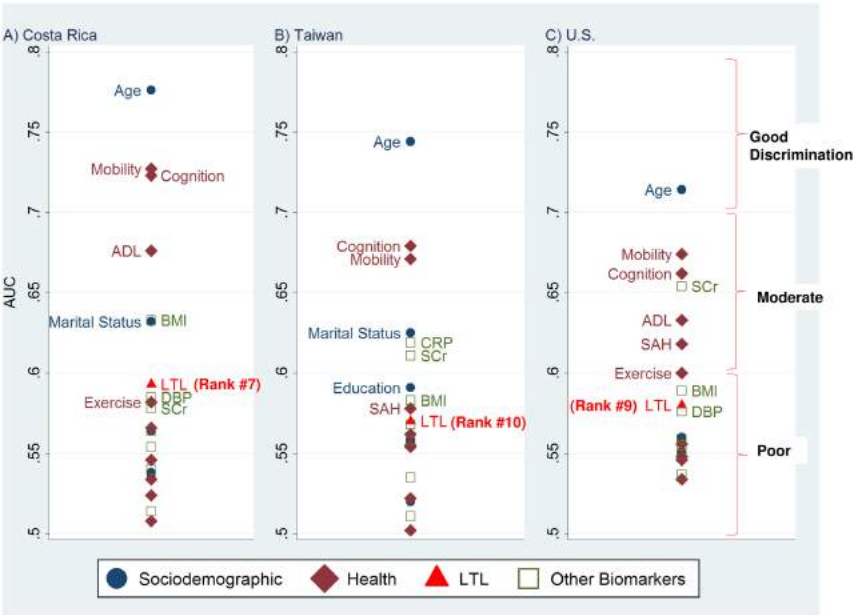
Telomere length can be altered by external factors



Current candidate aging biomarkers

Is telomere length a good biomarker of aging?

"telomere length had little discriminatory ability and under-performed many conventional predictors of mortality, including easily collected self-reported measures"



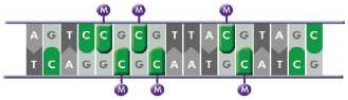
Glei DA, et al. (2016) Predicting Survival from Telomere Length versus Conventional Predictors: A Multinational PopulationBased Cohort Study. PLoS ONE 11(4): e0152486.

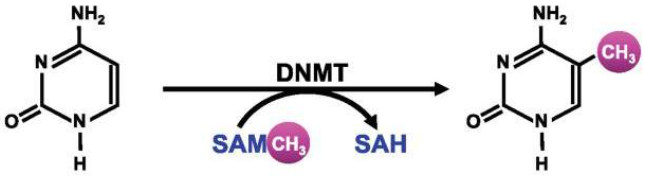
Current candidate aging biomarkers

DNA Methylation (Epigenetic Clock)

currently, most robust measure of biological age

Methylating cytosine nucleotides can alter gene activity





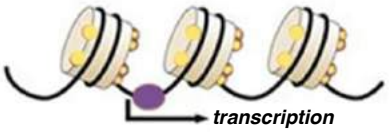
cytosine **5' Methyl-cytosine**

methylated DNA

Methylation

Acetylation

unmethylated



Not clear exactly what aspects of aging the clock measures

Current candidate aging biomarkers

DNA Methylation (Epigenetic Clock)

currently, most robust measure of biological age

very high correlation with chronological age

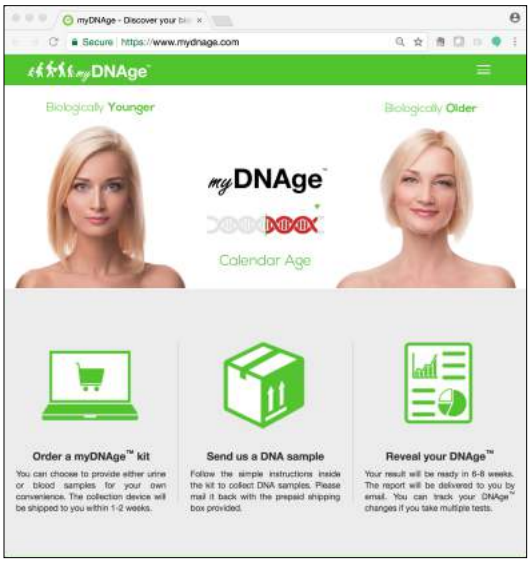
developed with large samples from multiple ethnic groups

2 different methylation calculations

Hovath Hannum

clock age varies across tissues

predicts all-cause mortality and many age-related diseases



Current candidate aging biomarkers

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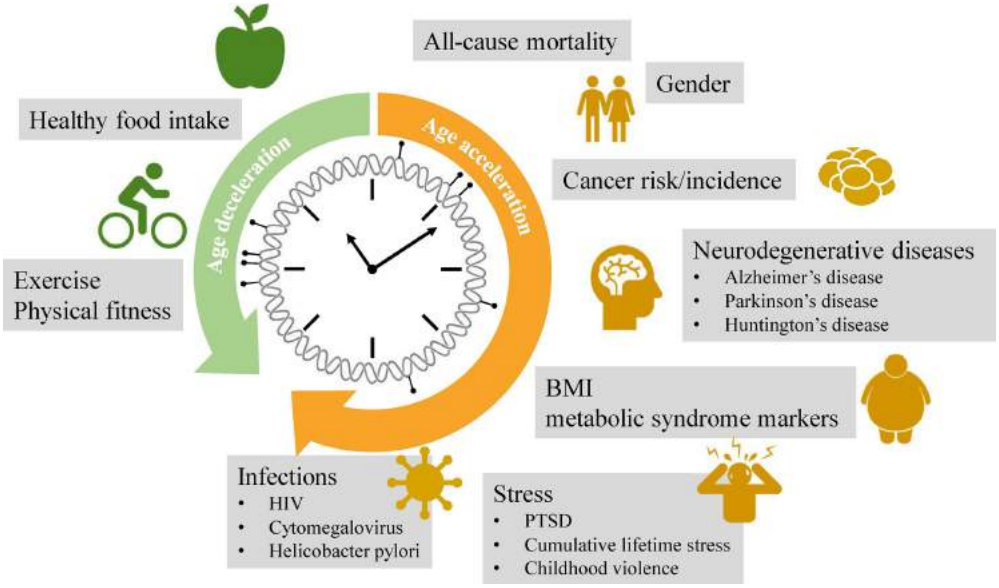

Declerck & Vanden Berghe (2018) Back to the future: Epigenetic clock plasticity towards healthy aging. Mechanisms of Aging and Development

what impacts health span?

Image credits: Jose Mosquera / Getty Images, Fotolia, Dreamstime, nigeriantoday

Next Week

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store information in DNA?

Feb 20 change my DNA?
create “designer babies”?

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March 6 help us reach and colonize Mars?