Cognitive Vitality Reports® are reports written by neuroscientists at the Alzheimer's Drug Discovery Foundation (ADDF). These scientific reports include analysis of drugs, drugs-in-development, drug targets, supplements, nutraceuticals, food/drink, non-pharmacologic interventions, and risk factors. Neuroscientists evaluate the potential benefit (or harm) for brain health, as well as for age-related health concerns that can affect brain health (e.g., cardiovascular diseases, cancers, diabetes/metabolic syndrome). In addition, these reports include evaluation of safety data, from clinical trials if available, and from preclinical models.

Epigenetic Clocks

Evidence Summary

Horvath and Hannum epigenetic clocks are highly correlative of age and time to death in population studies; however, it is unclear how valuable these clocks will be as a measure in individuals.

Neuroprotective Benefit: There is no evidence that blood epigenetic clocks correlate with Alzheimer's disease.

Aging and related health concerns: Evidence suggests that epigenetic clocks correlate with mortality and several disease states in population studies.

Safety: N/A

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What is it?

DNA methylation (DNAm) is one of three primary epigenetic mechanisms that control gene expression (the other two being histone tail modifications and microRNA regulation of mRNA). A methyl group (CH3) is attached to a cytosine DNA base pair, usually located next to a guanine base pair (a CpG site), which modifies the packaging of the DNA and changes gene expression. Three DNA methyltransferases: DNMT1, DNMT3a and DNMT3b, primarily mediate DNAm. DNMT1 has a maintenance role – during DNA replication, it copies the methylation pattern of the original strand. DNMT3a and DNMT3b add methyl groups to new CpG sites (Sen et al, 2016).

Aging leads to global hypomethylation and local hypermethylation at gene promoter regions. Global hypomethylation with age is observed in a number of species including salmon, rats, mice, and humans (model organisms such as yeast, flies, and worms have no or little DNA methylation) (Sen et al, 2016; Horvath 2013).

DNAm is highly heritable but is also influenced by the environment and other factors in a person's life. In a twin study, Horvath (2013) reported that the correlation of DNAmAge (see epigenetic clocks below) between twins was 100% in newborns but only 39% in elderly individuals (avg. age = 63 years).

Epigenetic Clocks

Epigenetic clocks are built by analyzing the global methylation changes of individuals over a wide range of ages to find certain CpG methylation states that correlate with age. For example, Horvath (2013) studied 21,369 CpG sites in 39 data sets to "train" his epigenetic clock (i.e. to find out which CpG sites best correlated with age). From this training set, he identified 353 CpG sites and then validated the clock using an additional 31 data sets. The Horvath clock accurately predicted age (correlation = 0.96; mean error = 3.6 years) in multiple cell types including whole blood, peripheral blood mononuclear cells, cerebellar samples, occipital cortex, buccal epithelium, colon, adipose, liver, lung, saliva, and uterine cervix. Horvath (2013) reported that DNA methylation age (DNAmAge) had the following properties: it was close to zero for embryonic cells and iPSCs, it increased with cell passage number, and it gave rise to a highly heritable measure of age acceleration. Some cell types did not correlate with DNAmAge (breast tissue, uterine endometrium, dermal fibroblasts, skeletal muscle tissue, and heart tissue).

The other epigenetic clock in widespread use is the Hannum clock. Hannum et al (2013) sampled whole blood from 656 individuals aged 19-101 and used 71 CpG sites for their clock. It accurately predicts age (correlation=91%; error=4.9 years) though not as well as the Horvath clock. Hannum et al (2013) reported that gender but not BMI contributed to aging rate with men aging approximately 4% faster.

Nearly all the CpG sites in the Hannum clock lie within or near genes with known functions in aging-related conditions including Alzheimer's disease, cancer, tissue degradation, DNA damage, and oxidative stress.

In general, the Horvath clock under-estimates age by a couple of years and the Hannum clock over-estimates age by a few years (Christiansen et al, 2016; Marioni et al, 2015). Although a few other clocks have been described, they are not as well validated. All the following studies use either the Horvath or Hannum clocks. Studies in disease states often examine epigenetic clock acceleration, i.e. whether an individual with a disease state has an expected age that is greater than his/her biological age.

Neuroprotective Benefit: There is no evidence that blood epigenetic clocks correlate with Alzheimer's disease.

Types of evidence:
- 3 studies in post-mortem Alzheimer's disease tissue
- 2 studies of cognitive decline using blood
- 2 studies comparing blood cells and brain tissue

Human research to suggest DNAmAge can predict dementia, cognitive decline, or cognitive function?
DNAm at certain CpG sites in post-mortem tissue is associated with the burden of Alzheimer's pathology (De Jager et al, 2014; Yang et al, 2015). Using tissue from the prefrontal cortex of 700 individuals, Levine et al (2015) reported that DNAmAge (Horvath clock) was associated with diffuse plaques, neuritic plaques, and amyloid load. In patients with Alzheimer's disease, every half a year increase in DNAmAge was associated with one unit decrease in global cognitive function, working memory, and episodic memory. However, there was no association for non-Alzheimer's patients in any cognitive measure (Levine et al, 2015).

These studies were conducted in post-mortem tissue. To be a good biomarker for Alzheimer's disease, less invasive measures will be required. No studies have measured DNAmAge acceleration in the blood of Alzheimer's patients. However, in blood samples from a cross-sectional study in elderly individuals, DNAmAge acceleration was significantly associated with lower cognitive scores but did not predict cognitive decline in a 6 year follow up (Maroni et al, 2015). In addition, there was no association between DNAmAge acceleration and cognition in a monozygotic twin study in middle-aged individuals (Starnawskaet et al, 2017). Preliminary studies suggest that inter-individual variation of DNAm in the

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blood is not a strong predictor of inter-individual DNAm variation in brain tissue (Hannon et al, 2015; Yu et al, 2016). Future studies in longitudinal cohorts will be required to determine whether DNAmAge acceleration is associated with Alzheimer's disease. However, the association of Alzheimer's with other co-morbidities may confound these results.

APOE4 interactions:
None reported

Aging and related health concerns: Evidence suggests that epigenetic clocks correlate with mortality and several disease states in population studies.

Types of evidence:
   * Multiple longitudinal and cross-sectional studies correlating DNAmAge acceleration with mortality and disease state

Mortality
Both the Horvath and Hannum clocks are highly correlative with age, and multiple studies show that DNAmAge acceleration is associated with increased mortality. In a study of 4,658 individuals from 4 cohorts (avg. age = 69.1), each 5-year increment of DNAmAge acceleration predicted a 16% (Hannum) and 9% (Horvath) increased risk of mortality (Maroni et al, 2015). In a study of 86 twins (avg. age = 76.4), each 5-year increment of DNAmAge acceleration predicted a 35% (Horvath) increased risk of mortality. In addition, the twin with the oldest DNAmAge had a 69% greater probability of dying first (Christiansen et al, 2016). In a study of 1,863 individuals (avg. age. 62.5), each 5-year increment of DNAmAge resulted in a 23% (Horvath) and 10% (Hannum, non-significant) increased risk of mortality (Perna et al, 2016). Finally, in a meta-analysis of 13,089 elderly individuals, using a novel method that incorporates both DNAmAge acceleration and white blood cell count, a 10-year increase in DNAmAge acceleration resulted in a 48% (Hannum) increased risk of mortality (Chen et al, 2016).

These results differ because of the nature of the cohorts (populations, follow-up, etc.) and the different covariates used to control the analyses. However, there is a consistent increased risk of mortality with DNAmAge acceleration that seems to be independent of sex, age, and disease status.

Longevity

DNAmAge of semi-supercentenarian offspring was 5.1 years younger than age-matched controls. DNAmAge of semi-supercentenarians was on average 8.6 years lower than their chronological age (Horvath et al 2015).

Frailty

DNAmAge acceleration of 12 years was associated with one additional deficit on a frailty index (based on 34 deficits) (Breitling et al 2016).

Telomere length

DNAmAge and telomere length were either not associated (Breitling et al, 2016) or weakly associated (Marioni et al, 2016) with each other. The two are independent measures of mortality risk. One standard deviation increase DNAmAge was associated with a 22% increased mortality risk. One standard deviation increase in telomere length was associated with an 11% (non-significant) decrease in mortality risk. Telomere length explained 6.6% of the variance in age while DNAmAge explained 17.3% (Marioni et al, 2016).

CMV Infection

CMV seropositivity was associated with DNAmAge acceleration in nonagenarians (6 year acceleration) (Kananen et al, 2015).

Obesity

DNAmAge acceleration of 3.3 years (Horvath) in the liver was associated with each 10 unit increase in BMI. However, there was no association between BMI and DNAmAge of human blood, muscle, or adipose tissue (Horvath et al 2014).

Hypertension

DNAmAge acceleration was not associated with hypertension (Marioni et al, 2015) but was weakly, albeit non-significantly, associated with cardiovascular disease mortality (HR 1.19; 95%CI 0.98-1.43; Horvath) (Perna et al, 2016).

Diabetes

DNAmAge acceleration was not associated with diabetes (Marioni et al, 2015).

Cancer Mortality
DNAmAge acceleration was associated with a 22% (Horvath) increased risk of cancer mortality (Perna et al, 2016). In a set of cancer tissue samples, some showed DNAmAge acceleration while others showed DNAmAge deceleration (Horvath) (Horvath, 2013).

Lung Cancer/smoking
One standard deviation increase in DNAmAge, using a method that incorporates blood cell counts, was associated with a 2-fold increase in lung cancer risk in women smokers (avg. age = 65 years) over a 20 year follow up period. There were non-significant increases with former smokers and non-smokers (very slight increase). The association was stronger for older individuals (Levine et al 2015). Smoking status, per se, was not associated with DNAmAge acceleration (Gao et al, 2016; Levine et al 2015).

Stress
DNAmAge acceleration was associated with cumulative stress (but not childhood maltreatment or current stress, alone) in an urban, African American cohort. A high number of CpG sites within glucocorticoid response elements were affected (Zannas et al, 2015).

Menopause
DNAmAge acceleration was associated with earlier menopause (whether natural or surgical) and longer time since menopause. However, it was difficult to ascribe a cause/effect relationship (Levine et al, 2016).

Safety: *NA.*
Epigenetic clocks are a biomarker that require a blood draw, thus there are no significant safety effects.

Sources and dosing:
There are no FDA approved tests for DNAmAge. All are currently used for research.

Research underway:
The development of epigenetic clocks is an active area of academic research. Though none are in development for FDA-approved clinical use.

Search terms:
Pubmed:
Epigenetic clock + Alzheimer, dementia, cognitive decline, cognition
Epigenetic age + mortality
Epigenetic clock [title/abstract]

Google:
Epigenetic clock, Horvath clock

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