



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.

Polygenic Risk Score

Evidence Summary

There is promise in the use of polygenic risk scores to identify the remainder of genetic risk in chronic disease or to identify patients at higher risk of disease, but more validation is needed, especially in non-Caucasian populations.

Neuroprotective Benefit: Polygenic risk scores may be used to calculate future risk of Alzheimer's disease; however, more validation is needed, and future studies should incorporate environmental factors and non-Caucasian populations.

Aging and related health concerns: The evidence that polygenic risk scores may show who will benefit with therapies because of high genetic risk is compelling.

Safety: The only safety issue with polygenic risk scores is misclassification of disease risk if the score is not further validated, especially in non-Caucasian populations.

Availability: Two companies in commercial development for Alzheimer's disease (Cytos and Vivid Genomics); cardiovascular risk calculators are being developed.	Dose: NA	Chemical formula: NA
Half life: NA	BBB: NA	
Clinical trials: None	Observational studies: NA	

What is it?

Beyond ApoE4, genome wide association studies (GWAS) have identified about 20 genes significantly associated with late onset Alzheimer's disease (ABCA7, BIN1, CD33, CLU, CR1, CD2AP, EPHA1, MS4A4, PICALM, HLA-DRB5/DRB1, SORL1, PTK2B, SLC24A4/RIN3, ZCWPW1, SELF1, NME8, FERMT2, CASS4, INPP5D, and MEF2C). Most of these genes only slightly increase the risk for Alzheimer's (OR 1.2-1.8), and cluster around common pathways involved with inflammation, cytoskeletal organization, and cholesterol metabolism ([Escott-Price et al, 2017](#)).

Recently, investigators have started to develop polygenic risk scores (PRS) to improve prediction of disease risk from genetic data. To develop a PRS, researchers use a training data set to assign weights to individual SNPs based on how much they contribute to disease risk. Then they test the PRS in a validation data set to confirm the sensitivity, specificity, and area under the curve (AUC) of a receiver operating characteristic curve (AUC is the probability that a randomly selected individual with a disease will have a higher risk than a randomly selected individual without the disease). An AUC of 50% has no predictive power, <60% low predictive power, and 60-70% modest predictive power. Generally, AUCs >80% are considered good ([Torkamani et al, 2018](#)). PRS can be developed based on certain types of SNPs or SNPs that reach genome-wide significance in GWAS studies. For Alzheimer's disease, this would lead to the 20 SNPs currently associated with Alzheimer's to be incorporated in the PRS score. In some studies, investigators lower the threshold for significance in GWAS studies. Although this may cause a number of genes that are not truly related to disease progression (i.e. false positives) to be picked up in the PRS, it increases the power of the PRS.



One caveat to note with PRS (and GWAS studies in general). It is not known whether many of the SNPs directly contribute to disease risk because they might be in linkage disequilibrium with an actual causative gene (the actual causal gene is located near the SNP but is passed along with it at birth). This has one major implication for PRS – scores developed in one population (e.g. Caucasians) may not be applicable to another population (e.g. African populations) because of genetic background. Most PRS are based on individuals of European ancestry.

Neuroprotective Benefit: Polygenic risk scores may be used to calculate future risk of Alzheimer's disease; however, more validation is needed, and future studies should incorporate environmental factors and non-Caucasian populations.

Types of evidence:

- 8 studies looking at PRS and risk of Alzheimer's disease
- 7 studies looking at PRS and Alzheimer's disease biomarkers

Human research to suggest prevention of dementia, prevention of decline, or improved cognitive function?

Most Alzheimer's PRS have used data from the International Genomics of Alzheimer's Project (IGAP), a large dataset of 17,008 Alzheimer's cases and 37,154 controls. Participants were genotyped using high-density SNP microarrays from Illumina or Affymetrix with data from 7,055,881 SNPs. Participants are from the United States, the UK, and the EU.

In the first study to use the IGAP data, [Escott-Prince et al \(2015\)](#) reported that their PRS could predict Alzheimer's disease with a sensitivity of 0.704, specificity of 0.703, and an AUC of 78%. This analysis included age, sex and ApoE4 status in the model. When excluding SNPs near the 20 genes found in previous Alzheimer's GWAS studies and ApoE, the association of the remaining SNPs with Alzheimer's was still significant suggesting there is remaining genetic influence beyond previously known Alzheimer's genes.

[Escott-Prince et al \(2017\)](#) followed up this study with another using a PRS from the same data set in pathologically confirmed Alzheimer's cases (1,011 cases and 583 controls). They reported an improved prediction accuracy with an AUC of 84% (95%CI = 82-86%). Since Alzheimer's disease is also influenced by age, sex, and lifestyle factors, genetic data can only predict the risk of Alzheimer's disease to a certain



extent, and [Escott-Prince et al \(2017\)](#) conducted another analysis to estimate the maximum prediction accuracy using genetic data. They reported $AUC_{MAX} = 82\%$. This suggests that current GWAS studies capture most of the genetic data that increase the risk for Alzheimer's ([Escott-Prince et al, 2017](#)). In the future, the AUC may be improved by adding further environmental or biomarker data. Additionally, although most of the heritability can be explained by the current GWAS studies, there still may be rare unknown variants that may increase risk. Exome-wide sequencing studies are ongoing to identify additional rare risk genes ([Alzforum](#)).

Investigators from Harvard have also used PRS to look at Alzheimer's risk and amyloid load. PRS were also built from the IGAP data set and were tested from individuals in the Alzheimer's Disease Neuroimaging Initiative (ADNI). In elderly individuals without dementia, elevated PRS was associated with decreased memory, smaller hippocampal volume, greater cognitive decline, and increased risk for dementia over three years ([Mormino et al, 2016](#)). Higher PRS was also associated with increased amyloid PET and a trend toward decreased CSF $A\beta$. Interestingly, higher PRS was associated with smaller hippocampal volume in healthy young participants (18-35). This result was found when they included many SNPs below GWAS-level significance (16,123 SNPs) but not when the PRS was restricted to GWAS-level significance SNPs (18 SNPs). Notably, the association between PRS and Alzheimer's biomarkers was small, accounting for only 1-3% of the variance in older adults without dementia.

In a follow up study, [Ge et al \(2018\)](#) reported that the PRS was higher in amyloid positive individuals, though the associations between amyloid at baseline and PRS were weak. Additionally, PRS was higher in amyloid positive Alzheimer's and MCI patients compared to cognitively normal amyloid positive patients. Higher PRS was not association with amyloid accumulation but was associated with cognitive decline in the amyloid group, explaining 8-10% of the variation in the rate of decline. These results were significant after controlling for the effect of ApoE status, suggesting that PRS explains variance beyond ApoE4.

PRS scores have also been associated with progression to Alzheimer's disease and age of onset. [Tan et al \(2017\)](#) reported that PRS predicted risk of progression from cognitively healthy to Alzheimer's disease (HR = 2.36; 95%CI 1.38-4.03) and MCI to Alzheimer's (HR = 1.17; 95%CI 1.02-1.35). The age of onset for individuals with a low PRS (~16 percentile) was 85 while the age of onset for individuals with a high PRS (~84 percentile) was 78. PRS also predicted rate of decline. In another study in ApoE3/ApoE3 patients, compared to individuals with a PRS in the top decile, those in the bottom decile had an expected age of onset that was more than 10 years earlier (HR: 3.34; 95%CI 2.62-4.24). The PRS score strongly predicted



the age of onset and was significantly associated with amyloid plaques, tau tangles, cognitive function, CSF amyloid, CSF tau, and volume loss in the hippocampus ([Desikan et al, 2017](#)).

Other PRS studies have reported an ability to predict individuals with sporadic early-onset Alzheimer's disease (<65 years; sensitivity 59.1%, specificity 72.9% [[Chowdhury et al, 2018](#)] and OR = 6.44 with ApoE effects added [[Cruchaga et al, 2018](#)]), MCI in adults in their 50s ([Logue et al, 2017](#)), cognition in healthy elderly ([Marioni et al, 2017](#)), and hippocampal volume in young adults, Alzheimer's, and MCI patients ([Lupton et al, 2016](#); [Foley et al, 2017](#)). However, some conflicting results have been reported for CSF Alzheimer's biomarkers and hippocampal volume in young healthy patients ([Lupton et al, 2016](#); [Voyle et al, 2017](#)).

Other studies have looked at PRS associations using fewer SNPs. [Morgan et al \(2017\)](#) used a full PRS model and a model using immune-specific Alzheimer's disease SNPs in Alzheimer's patients and reported that out of 6 plasma analytes measured only clusterin was significantly correlated with PRS while C1inh and clusterin were positively correlated with an immune-specific PRS. [Schultz et al \(2017\)](#) built a PRS derived from ApoE4, Clu, and ABCA7 and reported that a high PRS in asymptomatic patients (age 61) was associated with lower A β 42/40, higher t-tau/A β 42, and higher p-tau/A β in the CSF. These associations were diminished in individuals with a higher cardiorespiratory fitness suggesting a beneficial effect of cardiorespiratory fitness in individuals with a high PRS.

APOE4 interactions:

Studies suggest that PRS adds predictive value to Alzheimer's risk beyond ApoE4 status.

Ageing and related health concerns: The evidence that polygenic risk scores may show who will benefit with certain therapies is compelling.

Types of evidence:

- 3 studies on CVD
- 2 studies on effects of drug treatment in CVD
- 1 study on effect of lifestyle in CVD
- Studies on cancer risk



Cardiovascular disease

[Khera et al \(2018\)](#) developed a PRS based on the UK Biobank population that predicted the risk of coronary artery disease (CAD) equivalent to the risk in patients with familial hypercholesterolemia (FH, present in 0.5% of the population; 3-fold increased risk). Using their score, they reported that 8% of the population would have an OR>3.0; 2.3% of the population would have an OR>4.0; and 0.5% of the population would have an OR>5.

Although the use of PRS is potentially compelling, several criticisms have been raised on the methodologies of the technique ([see this article from Nature](#)).

Despite the controversy, there is evidence that individuals with a high PGS may benefit from more intensive therapy. Using 50 SNPs that reach genome-wide significance, [Khera et al \(2016\)](#) divided individuals into high, medium, and low genetic risk from 3 cohort studies that grouped patients (avg age 55) into favorable, intermediate, and unfavorable lifestyles. Compared to individuals with low genetic risk and a favorable lifestyle, high genetic risk and favorable lifestyle were associated with risk for coronary events (HR = 1.90); low genetic risk and unfavorable lifestyle were associated with risk for coronary events (HR = 1.82); and high genetic risk and unfavorable lifestyle were associated with coronary events (HR = 3.50). This suggests that it is even more important for patients with a high genetic risk to have a favorable lifestyle, but even if they do, more intensive therapy may be needed to decrease risk of CAD. One caveat is that baseline characteristics suggest that those in the high genetic risk group had a slightly increased risk for having a family history of premature CAD (2-8% more) and increased baseline LDL levels (5-10mg/dl) but no other changes in cardiovascular risk factors.

Another study from [Mega et al \(2015\)](#) looked at the benefits of statin therapy from two primary prevention RCTs (JUPITER and ASCOT) comparing individuals with low genetic risk vs high genetic risk using 27 SNPs that reached genome-wide level significance. In the placebo group, high genetic risk was associated with an increased risk of coronary heart disease (HR: 1.72; 95%CI 1.52-1.92). Statin therapy non-significantly reduced risk in the low genetic risk group (HR: 0.66; 95%CI 0.34-1.27) but was even more beneficial in the high genetic risk group (HR: 0.53; 95%CI 0.37-0.71). There was a 0.2-2% increased absolute risk reduction in the high genetic risk group compared to the low genetic risk group reducing the number needed to treat (NNT) to prevent one event in 10 years from about 60 in the low genetic risk group to 22 in the high genetic risk group, suggesting that patients with high genetic risk gain more benefit from statin therapy.



Another study repeated this analysis using 67 SNPs that had reached genome-wide significance (updated from the previous 27 SNPs) and adding a third primary prevention trial (WOSCOPS) and reported a 46% relative risk reduction in the group with the highest quintile genetic risk compared to a 26% relative risk reduction in the other groups. The absolute risk reduction with statin therapy in the highest genetic risk group was 3.5% (95%CI 2.0-5.1) and 1.3% (95%CI 0.6-1.9) in the other groups ([Natarajan et al, 2017](#)).

Note that all three were primary prevention studies: WOSCOPS enrolled patients with hypercholesterolemia, ASCOT enrolled patients on anti-hypertensives and cholesterol levels up to 251.35mg/dl, and JUPITER enrolled patients with high hsCRP (2mg/L or higher) and cholesterol levels lower than 130.32mg/dl.

Another study developed a PRS based on 49,310 SNPs in the CARDIoGRAMplusC4D consortium and tested the score on five prospective cohorts. High PRS was associated with increased risk of CHD (ranging from HR = 1.28-1.74). Men in the top 20% of the PRS had a 10% increased cumulative risk of CHD 12-18 years earlier than those in the bottom 20%. A high PRS was partially attenuated by low systolic blood pressure, low cholesterol, and not smoking ([Abraham et al, 2016](#)). However, another study using the CARDIoGRAMplusC4D consortium data reported that PRS using 152 SNPs did not improve prediction of prevalent CHD better than traditional risk factors. They suggest it might be because that built the score on prevalent CHD rather than incident CHD ([de Vries et al, 2015](#)).

Other diseases

[Khera et al \(2018\)](#) also identified PGS that would identify individuals at risk for atrial fibrillation, type 2 diabetes, inflammatory bowel disease and breast cancer with risks equivalent to monogenic mutations

PRS have been developed by other groups looking at some of these diseases with, for instance, breast cancer risks estimating an increased risk of OR = 1.38-3.36 in the groups with the highest quintile PRS score ([Mavaddat et al, 2015](#); [Li et al, 2017](#)). Cancer PRS are particularly interesting as they can be used to identify populations of patients who should be screened for cancer at an earlier age. For instance, a breast cancer PRS was developed, in conjunction with other clinical risk factors, to identify 16% of the population who would benefit from a mammogram at 40 years of age rather than 50 years. This was also seen for colorectal cancer where individuals in the highest decile of a PRS would be recommended to be screened at the age of 42 rather than 52 in the lowest decile. A prostate cancer PRS found that individuals in the top 20% of the PRS accounted for 42% of aggressive prostate cancers ([Torkamani et al, 2018](#)).



Safety: The only safety issue with polygenic risk scores is misclassification of disease risk if the score is not further validated, especially in non-Caucasian populations.

Types of evidence:

- One study comparing PRS in different patient populations

The main safety risk associated with PRS is the potential for misclassifying the risk of disease from someone with a different ancestry than the discovery cohort. [Reisberg et al \(2017\)](#) used a published PRS for CHD that was built on a population of European ancestry (Abraham et al, above). They then looked at the risk distribution in other populations including Estonia, Europe, America, South-Asia, East-Asia and Africa. They found very different risk distributions depending on the population examined. Their explanation for the distribution differences is that since SNPs do not always identify causal genes, the linkage disequilibrium between causal and associated SNPs could vary based on the population of interest. Therefore, before using a PRS to calculate risk, the score should be built based on an individual's ancestry.

Research underway:

This is an active area of research. Most of the studies have been published in the last three years, and there will likely be many more studies published.

Search terms:

Polygenic risk score + Alzheimer, cardiovascular, longevity

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If you have suggestions for drugs, drugs-in-development, supplements, nutraceuticals, or food/drink with neuroprotective properties that warrant in-depth reviews by ADDF's Aging and Alzheimer's Prevention Program, please contact INFO@alzdiscovery.org. To view our official ratings, visit [Cognitive Vitality's Rating page](#).