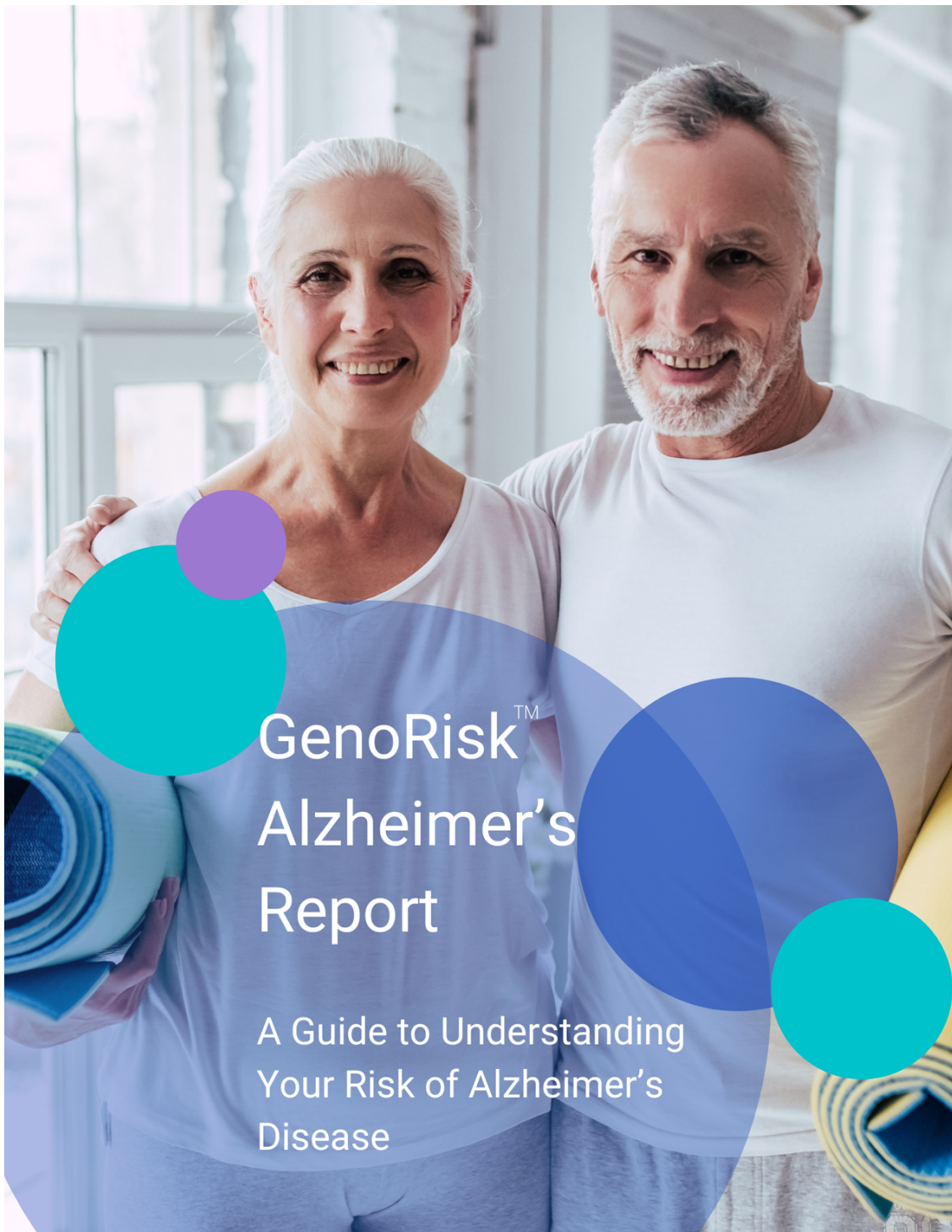


Name: Jane Sample
Date of Birth: 11/09/1948
Gender at Birth: Female

Ethnicity: White
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About GenoRisk™

GenoRisk integrates genetic insights from your DNA with the latest research on how these genetic factors affect your likelihood of developing Alzheimer's disease. GenoRisk incorporates 31 single nucleotide polymorphisms (SNPs) from 23 genes known to be related to Alzheimer's disease into a single score. This score provides important information about your non-modifiable (genetic) risk for Alzheimer's disease, and your report will also explain modifiable lifestyle factors that you can address with your healthcare provider that may reduce your risk.

What are genetics?

Genetics is the study of different traits that are passed on from your parents through DNA. Deoxyribonucleic acid, or DNA, is the molecule within your cells that gives instructions to build the proteins needed for all of your body's functions. DNA is bundled into a total of 23 chromosome pairs; within these chromosomes are an estimated 20,000 to 25,000 genes.

DNA itself appears like a twisted ladder called a double helix. The sides of the ladder are made up of a phosphate molecule and a sugar molecule, deoxyribose. The rungs of the ladder are formed by nucleotides called "bases." There are only four nucleotide bases (A, C, G, T) and how they are arranged defines every aspect of who you are from a genetic perspective.

Surprisingly, humans share >99.9% of the same genetic code. The <1% that is unique involves changes to specific nucleotide bases, resulting in changes to specific genes.

These different nucleotide arrangements are known as "SNPs" or single nucleotide polymorphisms. Your unique genetic makeup is known as your genotype.

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What is Alzheimer's disease?

Alzheimer's disease is a progressive form of dementia that affects memory, language, problem-solving, and ability for self-care and accounts for 60-80% of all dementia cases. It affects an estimated 6.5 million Americans, a number that is expected to grow to 12.7 million by 2050.¹

Alzheimer's disease is associated with the accumulation of amyloid "plaques" and tau protein "tangles" in the brain, eventually leading to the dysfunction and death of neurons, the cells responsible for function and communication within the brain.

While there is no definitive treatment for Alzheimer's disease, there is now a better understanding of the risk factors. In recent years, new research regarding risk reduction and treatment of early disease has emerged.

What are the symptoms of Alzheimer's Disease?

Patients with Alzheimer's typically have some, but not all, of these symptoms, which include:

- Memory loss
- Behavioral changes such as agitation, delusions, and hallucinations
- Loss of interest in previously enjoyed activities
- Difficulty with problem solving
- Difficulty performing tasks that were previously easy
- Personality changes
- Loss of social skills and tendency to withdraw or isolate
- Language problems including forgetting names of people or familiar objects

It is important to note that GenoRisk™ predicts risk for the most common form of Alzheimer's disease, which is non-familial Alzheimer's disease. GenoRisk does not test for mutations in PSEN1, PSEN2, or APP, which are the genes associated with the rare familial form of Alzheimer's disease.

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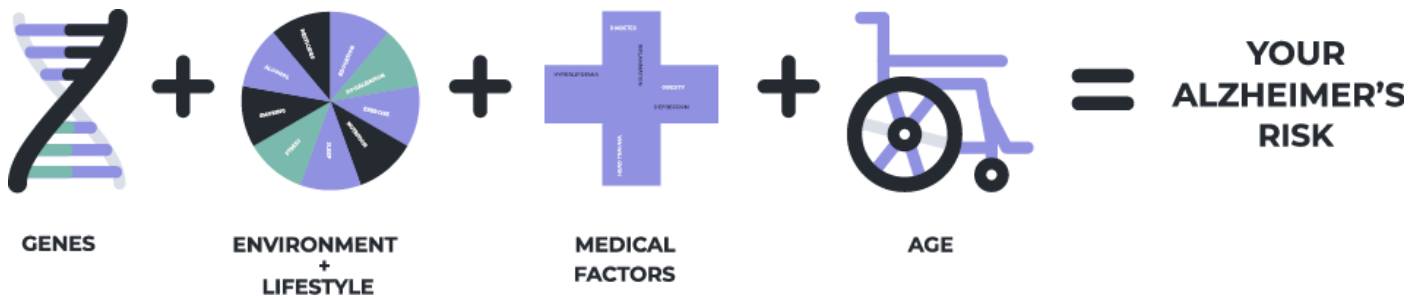
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What do we know about Alzheimer's disease?

While plaques and tangles are the pathological hallmarks of Alzheimer's disease, there are many other contributing factors that affect the development of the disease. Changes to the brain may begin decades before the disease is fully established and diagnosable, making risk-prevention strategies important early in life.^{3, 4}

For most people, the development of Alzheimer's disease is caused by a combination of both modifiable and non-modifiable factors. Non-modifiable risk factors include genetics, age, and gender. Modifiable risk factors include lifestyle factors such as diet, physical activity, sleep, and smoking, as well as some medical conditions.^{1, 5, 6} More details on these factors are provided later in this report.



Other factors contributing to Alzheimer's disease risk

Your GenoRisk™ score will give you important information about your genetic risk of developing Alzheimer's disease. The Take Action section at the end of your GenoRisk report will explain the many modifiable lifestyle factors that may reduce your risk.

Work with your physician to address any medical conditions you may have that are related to Alzheimer's disease such as high blood pressure, diabetes, sleep apnea, and thyroid disease. There is early evidence that managing these factors may also reduce risk for Alzheimer's disease, along with the lifestyle factors described later in the report.

GenoRisk is a risk-prediction tool, not a diagnostic test. If you are concerned about your Alzheimer's disease risk based on your GenoRisk Score, family history, or cognitive symptoms, discuss your concerns with your physician.

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The science behind your report

Your GenoRisk™ Score is based on a polygenic risk score or an estimate of the genetic risk of an individual for a specific disease or trait, in this case Alzheimer's disease, calculated by aggregating the effect of many common gene variants associated with the condition. GenoRisk incorporates 31 SNPs known to be related to Alzheimer's disease risk, including two SNPs in the APOE gene, the single most important genetic factor for Alzheimer's disease risk.¹ Your GenoRisk Score differs from other polygenic risk scores for Alzheimer's disease in that it was developed by evaluating multiple statistical models that incorporate multiple genes at one time, instead of simply combining risk estimates for single genes. The GenoRisk polygenic risk score is a risk-predictive test, which differs from a diagnostic test in that it provides the likelihood of future disease instead of providing a certain diagnosis. Having an understanding of your risk for developing Alzheimer's disease can help guide you on how to approach modifiable factors to reduce your risk.

Please note, GenoRisk does not analyze PSEN1, PSEN2, or APP - the genes associated with the rare familial form of Alzheimer's disease.

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Please read the important information below before viewing your results!



Low risk does not mean no risk.

Some people with a low genetic risk still develop Alzheimer's disease.



High risk does not mean certain development of Alzheimer's.

Some people with an increased genetic risk for Alzheimer's will never develop Alzheimer's disease.



Other factors influence your risk.

Learning your Alzheimer's-related genetic risk can be paired with your age, gender, medical health, and lifestyle habits to help assess your overall Alzheimer's disease risk, and identify areas where you may be able to take action to reduce your risk or delay the onset.



Knowledge is power.

Knowing your Alzheimer's disease risk may help you decide how aggressively you want to make lifestyle changes that can potentially improve your cognitive health.

YOUR POLYGENIC ALZHEIMER'S RISK SCORE



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Your GenoRisk™ Score result is 20

20

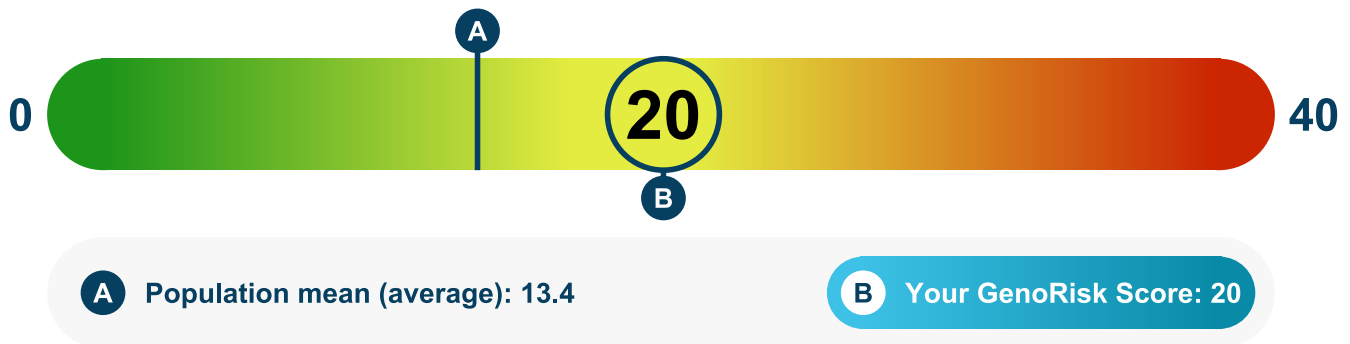
Your GenoRisk Score is 20. This score is calculated on a 0 to 40 scale and takes into consideration multiple gene variants that include both risk-associated and protective genes, including APOE.

GenoRisk Scale

The colored chart below provides an indication of genetic risk associated with Alzheimer's disease. Lowest risk scores are on the left (green) side, and highest risk scores are on the right (red) side of the chart. The vertical blue line indicates the mean (average) risk score for the population.

The GenoRisk Score calculations are based solely on your genetics, without considering the influence of age, gender at birth, or potentially modifiable risk factors such as medical conditions, lifestyle, or environment.

GenoRisk Scale



On the GenoRisk Alzheimer's Scale of 0-40, a score of 18 or higher indicates that an individual is in the 80th percentile or above for the population, meaning that their genetic risk for Alzheimer's disease is greater than at least 80% of the population.

If you receive a score of 18 or higher, we recommend that you speak with our healthcare partner for further clarification. To schedule a 15 minute telehealth appointment to discuss your result, please click on the link provided.

Your APOE genotype is e3e3

APOE is the most important individual genetic factor in Alzheimer's disease risk.⁸ Like all genes, you have two copies of APOE, one from your mother and one from your father. There are three variants of the APOE gene: APOE-e2, APOE-e3 and APOE-e4, and the e4 variant is associated with elevated Alzheimer's risk. Your APOE genotype is a component of your GenoRisk score, but many other genes are also incorporated into this score, which is a much more accurate predictor of Alzheimer's risk than APOE testing alone.

It is important to note that, similar to the overall GenoRisk score, your APOE result is not diagnostic of the disease. Having a high-risk result does not guarantee development of the disease and having a low-risk result does not exclude the possibility of the disease.

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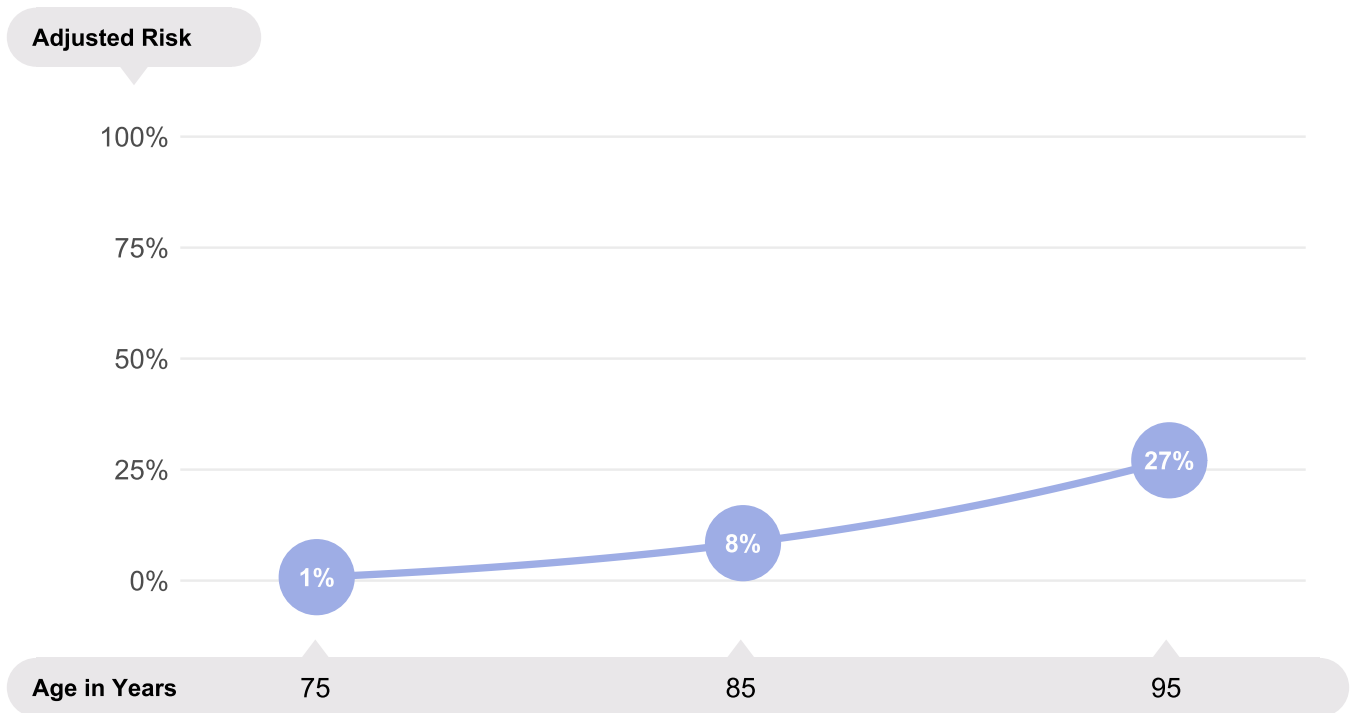
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Adjusted Risk for developing Alzheimer's disease

Your Adjusted Risk for developing Alzheimer's disease is your probability, or likelihood, of developing non-familial Alzheimer's disease by various specific ages. This is based on your gender at birth, current age, and GenoRisk™ Score. Please note that this probability score does not account for other factors such as medical conditions, lifestyle, environmental factors, and other genes outside of our analysis. Also remember that a high probability alone does NOT guarantee that you will develop Alzheimer's disease, nor does a low probability alone guarantee that you will never develop Alzheimer's disease.

For more information on your adjusted risk and comparison of your score to the population as a percentile rank, go to: <https://adxhealth.com/genorisk-percentile>

Probability of developing Alzheimer's disease by a given age



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GenoRisk™ Score

Genetic results are converted to a GenoRisk score by ADx Health using a proprietary algorithm. Single nucleotide polymorphisms (SNPs) used in the algorithm were chosen based on case-control study data from the Alzheimer's Disease Genetics Consortium (ADGC) database (2579 cases and 2578 controls). Several candidate models were compared using 10-fold cross-validation. The model selected was derived by using an elastic net with a logit link that chose age, age by sex interaction, and 31 SNPs including 2 APOE SNPs. The elastic net model performed the best of all candidate models with a Brier score of 0.207. To determine the population distribution of GenoRisk scores as well as mean and median population values, the algorithm was run on 2504 samples from the 1000 Genomes database. These samples include 26 worldwide and ethnically diverse populations.⁷

Adjusted Risk Score

The adjusted risk calculation took into consideration your GenoRisk Score as well as your current age and gender at birth. This was then converted to a probability or likelihood that you will develop Alzheimer's disease at a given age. Your Adjusted Risk Score should NOT be interpreted to indicate disease onset. It is a comparison of the genetics of individuals who developed Alzheimer's disease (cases) and people who did not develop Alzheimer's disease (controls) who participated in research studies. This score does not diagnose Alzheimer's disease, nor does it say with certainty whether you will develop Alzheimer's disease at a given age.

Limitations:

- This test does not diagnose Alzheimer's disease or dementia.
- This test does not test for mutations in PSEN1, PSEN2, or APP, the genes associated with the rare familial form of Alzheimer's disease.
- This test does not include all possible variants or genes for Alzheimer's disease.
- This test is not intended to be used by children under the age of 18.
- This test is not intended to assess genetic risk for non-Alzheimer's types of dementia, such as vascular dementia, Lewy body dementia, or frontotemporal dementia.

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Take Action!

Lifestyle and other factors can also influence your chances of developing Alzheimer's disease.

Consult with a healthcare professional before making any major lifestyle changes.



Stress



Exercise



Sleep



Nutrition



**Brain
Stimulation**



**Social
Connection**

Take Action

As you are evaluating which lifestyle factors you want to address, remember that it is not realistic to change them all at once. You are more likely to have lasting success implementing and maintaining behavior changes if you don't try to change them all at once but rather in small, incremental steps. You can work with your healthcare provider to identify which of your lifestyle behaviors are the most in need of modification and are going to be the easiest for you to change. This information can be used to develop a list of priority behaviors to change.

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Brain Impacts of Stress

Chronic and excessive stress may negatively impact your health, including your cognitive health. Learning to cope with stress is an important step in reducing your risk for Alzheimer's disease. Stress management techniques come in many forms, including relaxation exercises, behavioral changes, and social support:

Relaxation techniques:

- Yoga
- Stretching
- Meditation
- Mindfulness
- Progressive muscular relaxation
- Deep breathing
- Journaling
- Art or music therapy

Behavioral changes to reduce stress may include:

- Stop smoking
- Reduce alcohol intake
- Reduce caffeine intake
- Increase physical activity
- Get adequate sleep
- Develop routines

Support can include:

- See a therapist for one-on-one support
- Join a support group
- Socialize
- Interact with animals



Experiment with different stress management techniques to see which one(s) work best for you, because including daily stress management in your routine is important for brain health.

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Aerobic Exercise Benefits the Brain

Aerobic exercise increases your heart rate and breathing rate, raises your body temperature and strengthens your heart and lungs. Examples of aerobic exercises include walking, bicycling, swimming, dancing, doing yardwork, or any other activity that moderately increases your breathing and heart rate and may cause you to sweat. Participating in regular aerobic exercise is associated with improved cognition, lower blood glucose and insulin levels, reduced levels of inflammation, improved sleep, and reduced stress and anxiety.

Strength Training and Brain Health

Strength training maintains muscle strength and reduces the risk for falls and broken bones. Strength training combined with aerobic exercise may have a greater impact on cognitive health than aerobic exercise alone. Examples of strength training include using weights, resistance bands, or exercises that use your own body weight such as push-ups, squats, and lunges.¹⁰

Exercise Prescription

Speak with your physician about your current health status before you begin any exercise program. Consider asking for a referral to a physical therapist to help you develop an exercise routine. The following guidelines can be used to develop your exercise routine:¹¹

Frequency:

- Participate in aerobic exercise 3-5 days per week
- Participate in strength training at least 2 non-consecutive days per week

Intensity:

- Aim to reach a moderate intensity level, which is the level that should allow you to talk comfortably or sing along with a song without difficulty or gasping for breath.

Time:

If you are not currently exercising, it is important to begin slowly. Work up to the following goals:

- 150 minutes, or 2½ hours, of total aerobic exercise each week
- Over time, increase your goal to 300 minutes, or 5 hours, each week for the greatest benefit

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Sleep and Cognitive Health

Sleep is critical for learning, forming memories, and saving memories into long-term storage. Poor sleep may be both a cause and a symptom of Alzheimer's disease.^{12, 13}

Most adults function best with 8 hours of sleep at night. The ability to sleep 7 to 8 hours at one time may decline with age.

Signs of inadequate sleep include:

- Feeling tired when you wake up
- Regularly feeling tired throughout the day
- Relying on caffeine to make it through the day
- Frequently 'sleeping in' on the weekends
- Having difficulty with focus, concentration, or memory
- Falling asleep immediately at night

Creating a Sleep Routine

Having a sleep routine and creating a healthy sleep environment can help you improve your quality of sleep. **Follow these guidelines to develop your bedtime routine:**

- Go to bed and get up at about the same time each day
- Sleep in a bedroom temperature that is 65 degrees Fahrenheit
- Limit artificial light coming from house lights or screens for 1-2 hours before bedtime
- Play soothing sounds such as calming music, guided imagery, nature sounds, or white noise before bed or if you wake in the middle of the night
- Limit napping to no more than 30 minutes during the day
- Limit caffeine intake to 1-2 cups of coffee or tea consumed before noon. Be aware of other sources of caffeine including chocolate, soft drinks, and some medications and supplements
- Finish your last meal at least 3 hours before you go to bed to improve digestion and sleep
- Refrain from drinking alcohol before bed
- Do strenuous exercise earlier in the day. Yoga or other stretching exercises may be calming closer to bed
- Avoid smoking

Note: some medical conditions may decrease sleep quantity and sleep quality. Please speak with your doctor to address any medical causes of inadequate sleep.

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The importance of diet

Nutrition plays an important role in cognitive health. Following a brain-healthy diet can help manage blood sugar and inflammation, and provides your body and brain with the nutrients it needs to function at its best.

Both the Mediterranean Diet¹⁴ and the MIND diet¹⁵ have been shown to improve cognitive function and decrease risk of Alzheimer's disease.

The Mediterranean Diet

The Mediterranean Diet focuses on:

- Adequate intake of vegetables, fruits, legumes (beans and lentils), whole grains, olive oil, fish, and nuts and seeds
- Limited intake of dairy products and meats
- Regular but moderate intake of alcohol

The MIND Diet

The Mediterranean-DASH Intervention for Neurodegenerative Delay (MIND) Diet is a combination of the Mediterranean diet and the Dietary Approaches to Stop Hypertension (DASH) diets.

The foundation of the MIND diet includes:

- Daily intake of vegetables and leafy greens
- Intake of nuts 5 or more times per week
- Berries 2 or more times per week
- Beans 3 or more times per week
- Whole grains 3 or more times per day
- Fish at least once a week
- Poultry at least twice a week
- Olive oil daily
- One serving of wine daily

The MIND diet limits:

- Red meat
- Butter
- Cheese
- Sweets and pastries
- Fried and fast foods

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Brain Stimulation

It was once thought that the brain stopped growing and changing after childhood, but new research has shown that the brain continues to change and adapt to new information throughout the lifespan. The ability of the brain to make new connections is called “neuroplasticity.”¹⁶

As you learn new things throughout your life, your brain makes connections. The more you challenge your brain with new information, the more pathways you make, building up what is known as “cognitive reserve.” More cognitive reserve can prevent or slow memory decline as you age.

The following are associated with greater cognitive reserve and a lower risk of Alzheimer's disease:

- More years of education
- Speaking more than one language
- Playing a musical instrument
- Having a challenging profession

Activities that challenge your brain and improve cognitive reserve include:

- Reading
- Participating in discussion groups
- Doing puzzles
- Playing cards or board games
- Playing a musical instrument
- Learning a new language
- Using the computer
- Traveling
- Getting involved in a new sport or fitness class
- Taking a music, art, cooking, or craft class
- Experiencing art or theater events
- Using your non-dominant hand to do everyday tasks

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Social Connection

Making and keeping good social connections may improve your cognitive health. Staying engaged with others in conversation is a great way to challenge your brain and work on focus and attention. In fact, research has shown that regular social interaction can reduce the risk of dementia, a benefit that is greatest with daily social contact.¹⁷

There are a lot of ways to have regular social connections:

- Join a group of some kind, or if you belong to an organization you enjoy, try finding a way to get more involved
- Take a class at a local community college or community center to meet people and challenge your brain by learning something new
- Find a book club where you can challenge your brain to think about what you've read and participate in engaging conversation with other people
- Join a walking club, fitness class, or Silver Sneakers program, which can blend the benefits of social interaction and exercise
- Find a craft group at your local community or senior center as a way to meet other people and work on an activity that challenges your brain
- Become more involved in your religious organization's discussion, social, or volunteer groups
- Volunteer at your local hospital, school district or a local or national nonprofit

While interacting with people in person is the most ideal, there are other ways to find social engagement:

- Engage in virtual friendships using blog forums or social media
- Find an online support group that you find helpful
- Get a pet or visit a local animal shelter - caring for an animal stimulates your mind and provides a sense of companionship and purpose

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About Your Results

Genetic risk is only one component of your overall risk for Alzheimer's disease. The results of these tests do not provide a diagnosis of Alzheimer's disease nor are they a confirmation that you will or will not eventually develop Alzheimer's disease. Risk for sporadic (also known as non-familial) Alzheimer's disease is not influenced by genetics alone, as your lifestyle, environment, age, gender at birth, and other medical factors also contribute to your risk. For individuals experiencing memory loss or concerned about a family history of Alzheimer's disease, the Alzheimer's GenoRisk™ test will not diagnose Alzheimer's disease, nor will it tell you when or if you will develop Alzheimer's disease.

If you are concerned about your cognitive health or family history of Alzheimer's disease, you should speak to your healthcare provider about your concerns. Your GenoRisk report may be used by your healthcare provider as an additional resource for assessing your overall risk for Alzheimer's disease within the context of your medical history and other clinical, laboratory, or imaging tests. The results of this test do not diagnose or rule out a diagnosis of Alzheimer's disease now or in the future.

Test Description

Genetic testing is performed on self-collected saliva samples submitted to Avero Diagnostics, a CAP-accredited (#8446395), CLIA-certified (#50D2158817) laboratory. Regions surrounding SNPs of interest are first amplified by PCR, followed by differentiation of possible alleles by mass spectrometry. This is a laboratory-developed test (LDT) that has not been approved or cleared by the FDA.

Key Terms

- Deoxyribonucleic Acid (DNA) - The molecule within your cells that gives instructions to build the proteins needed for all of your body's functions. DNA is structured as a twisted ladder called a double helix. The sides of the ladder are made up of a phosphate molecule and a deoxyribose molecule. The rungs of the ladder are made up of nucleotide bases.
- Early Onset Alzheimer's Disease - Alzheimer's that occurs in individuals under the age of 65.
- Familial Alzheimer's Disease (FAD) - A rare form of Alzheimer's disease that runs in families caused by mutations in one of three genes: PSEN1, PSEN2 or APP. Almost all cases of familial Alzheimer's disease are "early onset" (beginning at less than 65 years of age), and many start in mid-life, in the 30s to 50s.
- Gene - Genes contain the specific information for human traits that are passed down to children from their parents.
- Genetics - The study of different traits that are passed to children from parents through DNA.
- Genotype - Genotype is the unique genetic makeup of an individual. Genotype can refer to just one gene or a set of genes.
- Late Onset Alzheimer's Disease - Alzheimer's that occurs in individuals over the age of 65.
- Nucleotide bases - Making up the "rungs" of the double-helix DNA "ladder" are one of four nucleotide bases: Adenine (A), Cytosine (C), Guanine (G), and Thymine (T). The specific combination of nucleotide bases determines the traits that are expressed.
- Polygenic - Determined by several different genes.
- Polygenic Risk Score - A genetic risk score calculated from a combination of multiple genetic factors.
- Single Nucleotide Polymorphism (SNP) - Pronounced "snips," SNPs are specific variants at individual nucleotide bases that exist in the human population.

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Name: Jane Sample
Date of Birth: 11/09/1948
Gender at Birth: Female

Ethnicity: White
Sample ID: ADX-123-456-789
Sample Collection Date: 09/25/2022

Date Received at Lab: 10/07/2022
Report Date: 10/12/2022 6:35 PM
Ordering Provider: Ryan Fortna, MD, PhD

Limitations

- This test does not diagnose Alzheimer's disease or dementia.
- This test does not test for mutations in PSEN1, PSEN2, or APP, the genes associated with the rare familial form of Alzheimer's disease.
- This test does not include all possible variants or genes for Alzheimer's disease.
- This test is not intended to be used by children under the age of 18.
- This test is not intended to assess genetic risk for non-Alzheimer's types of dementia, such as vascular dementia, Lewy body dementia, or frontotemporal dementia.

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Medical Directors: Kelly Lloyd, MD and Ryan Fortna, MD, PhD

Testing performed at Northwest Laboratory DBA Avero Diagnostics, 3548 Meridian St., Suite 101, Bellingham WA 98225
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