Alzheimer's Disease

Know your risk, Reduce your risk

ADx Health
KNOW MORE. BE MORE.

Alzheimer's disease (AD) is a slowly progressing neurodegenerative condition that affects memory, language, problem-solving, and ability for self-care. AD accounts for 60-80% of all dementia cases, affecting an estimated 5.8 million Americans in 2019, a number that is expected to grow to 13.8 million by 2050.[1] AD is associated with the accumulation of amyloid "plaques" and tau protein "tangles" in the brain, eventually leading to the dysfunction and death of neurons. These are the ultimate pathologic hallmarks of the disease, but numerous other upstream contributing factors affect development of the disease. The changes that occur in the brain which ultimately lead to cognitive dysfunction begin to develop decades before the disease is fully established and diagnosable.[2,3]

While there is currently no cure or definitive treatment for AD, there is now a better understanding of the risk factors, and in recent years new research regarding risk reduction and treatment of early disease has emerged. Risk for developing AD is now understood to be influenced by both modifiable and non-modifiable factors. Non-modifiable risk factors include genetics, age, and gender. Modifiable risk factors include lifestyle habits such as diet, physical activity, sleep, and smoking as well as other medical conditions including hypertension, diabetes, and sleep apnea.1-3

ADx Healthcare employs a comprehensive approach to risk assessment and risk reduction for Alzheimer's disease. Our mission is to enable individuals to "Know Your Risk, Reduce Your Risk" for this serious disease. For the assessment of non-modifiable risk factors, we have developed and validated a genetic assay known as "GenoRisk," which evaluates multiple genetic variants and employs a machine learning-based algorithm to provide the most accurate available genetic risk assessment for AD, then combines this with age and gender to produce a personal lifetime risk assessment. This information, paired with education about how lifestyle and medical factors augment this risk, provides a comprehensive and actionable program to individuals.

GenoRisk

Alzheimer's disease has a high degree of heritability, meaning that a significant component of an individual's risk for the disease is due to genetic factors, which account for approximately 50% of overall risk.[4] The gene with the greatest known effect on Alzheimer's disease risk is ApoE, which alone accounts for approximately one quarter of the heritability of AD,[4] but numerous other genes have now been identified which each provide smaller but significant contributions to AD risk. Most of these have been revealed over the last ten years using genome-wide association studies (GWAS).[5,6] These discoveries have also highlighted the importance of several biological pathways for disease pathogenesis.[7]

GenoRisk is a risk-predictive genetic test. Risk-predictive genetic tests differ from genetic tests. Diagnostic genetic tests are used to definitively determine whether an individual has (or will have) a disease.[8] Examples include assays of the Huntingdon (HTT) gene that causes Huntington's disease or the Presenilin and APP genes that cause a rare form of early-onset Alzheimer's disease known as Familial Alzheimer's disease (or autosomal-dominant Alzheimer's disease). In contrast, risk-predictive genetic tests do not provide a certain diagnosis or certain future diagnosis but rather provide a likelihood of future disease. As a non-modifiable risk factor, the genetic component of AD risk cannot be changed, but understanding it may help individuals and health care providers decide how aggressively they wish to pursue modification of the modifiable risk factors. This is similar to genetic testing for various cancer syndromes, which now has widespread acceptance in the medical field. For example, for patients determined to be at high risk for certain types of cancer based on genetics, the genetic risk itself cannot be changed, but understanding that risk can help health care providers determine which patients should be screened most aggressively or should be eligible for risk-reduction treatments (e.g. increased colonoscopy screenings in patients with Lynch syndrome, or prophylactic mastectomies and/or oophorectomies in patients with BRCA mutations).

Current risk reduction strategies for AD, which are described in greater detail below, are not as dramatic as prophylactic mastectomies nor as invasive as colonoscopies, but they do require serious commitment from patients as well as time and resources from the health care system; therefore, determining who is at above-average risk based on genetics may help determine which patients are most likely to benefit from these efforts. Furthermore, as drug-based preventive therapies begin to receive greater attention from both the pharmaceutical and the academic communities (after decades of drug trial failures that were focused on patients with established, late-stage AD), rational design of preventive clinical trials will also benefit from accurate risk stratification of patients using comprehensive genetic analysis. Genetic risk stratification may also be useful to determine which patients should receive preventive drugs once they are available, which is conceptually similar to "companion diagnostic tests" that are now commonly used to determine which cancer patients are eligible to receive targeted biologic therapy.[9]

The GenoRisk assay is based on 31 genetic variants (in 24 different genes) known to influence risk for AD, including ApoE. Although ApoE is the single most important genetic factor for AD risk and has been used on its own for several decades to stratify patients into various risk groups, there is a relatively wide range of risk within a given group of patients with the same ApoE genotype when other genetic factors are taken into account.9 In some cases, individuals with an average-risk ApoE genotype (i.e. the most common genotype, known as "e3/e3") may in fact have a higher overall genetic risk than some patients with a high-risk ApoE genotype ("e3/e4"), and vice versa (Figure 1).[10]

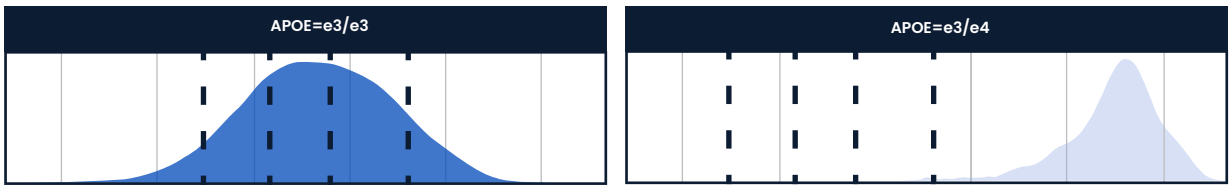

Figure 1. The wide spectrum of GenoRisk-calculated AD risk within selected ApoE genotype groups.

The GenoRisk score provides estimated genetic risk for AD on a 0-40 scale (Figure 2). The GenoRisk algorithm was developed using a case control study, with data from the Alzheimer's Disease Genetics Consortium (ADGC) database (2579 cases and 2578 controls). After developing the model using the case/control method, the model was validated using 2,504 samples from the 1,000 Genome Project. These 2,504 samples include 26 worldwide and ethnically diverse populations, including 661 subjects from Africa, 347 from the Americas, 504 from East Asia, 503 from Europe, and 489 from South Asia. In addition to the GenoRisk score, a lifetime risk score is produced which incorporates gender and current age (Figure 3).[10]

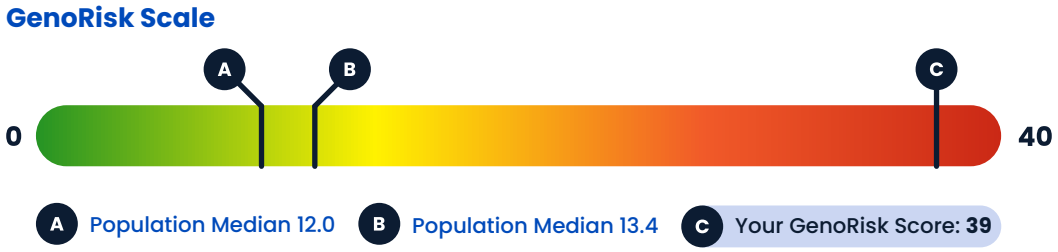

Figure 2. Sample patient GenoRisk score report visually representing calculated GenoRisk and population comparisons.

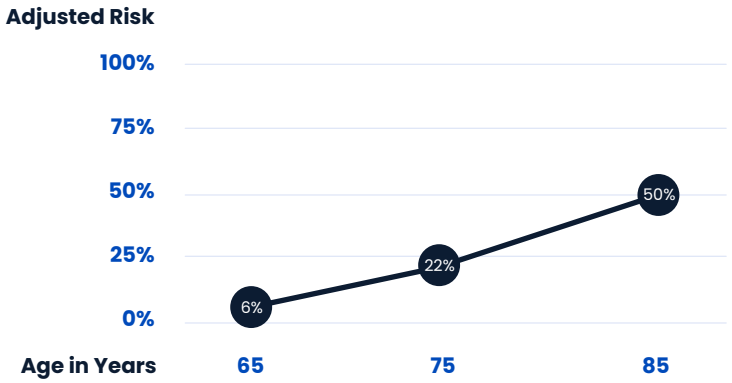

Figure 3. Sample patient GenoRisk score report visually representing adjusted lifetime risk at various ages.

The GenoRisk score differs from existing polygenic risk scores for AD in that it was developed by cross validating multiple statistical models that incorporate multiple genes at one time, instead of simply combining risk estimates for single genes. This results in a model that increases predictive accuracy and avoids the pitfalls of other polygenic risk scores, such as statistical overfitting. GenoRisk utilizes an elastic net model, a regularized regression machine learning model.[10]

Other Factors Contributing to Alzheimer's Disease Risk

Each person's risk for developing the most common form of AD (known as sporadic or non-familial Alzheimer's disease) is influenced by a combination of genetics, 1-5 age, gender at birth, medical conditions, environment, and lifestyle.[8,9]

Some of the medical conditions associated with Alzheimer's disease include: hypertension (especially mid-life hypertension), diabetes, obesity, and sleep apnea. There is early

evidence that identifying and 'correcting' these factors (e.g. improving diet and lifestyle choices and appropriately treating other medical conditions) may reduce an individual's risk for Alzheimer's disease. Changes in the brain that lead to Alzheimer's disease begin decades before symptoms appear, so monitoring for these conditions and intervening as early as possible is important.[8,9]

Lifestyle factors that affect the development and progression of Alzheimer's disease include diet, physical activity, sleep, social engagement,[8,9] and cognitive stimulation.[10] Many of these factors are predictive in mid-life, and it is likely that intervening prior to symptom onset will have the best chance of reducing risk.

As changing behavior is a challenge for many patients, motivation to make lifestyle changes may be driven by knowledge of a high risk. Additionally, education about the modifiable factors that contribute to the development of AD may also provide patients with the confidence they need to improve their health.

ADx Healthcare's Philosophy

Alzheimer's disease affects an ever-growing number of patients and families in our aging population. While preventive and therapeutic options have historically been absent or inadequate, exciting new research has now provided us with the ability to assess genetic risk factors and provide education about the role of other modifiable risk factors for AD in an effort to improve cognitive health and to potentially reduce risk for AD or delay the onset of the disease.

Since the changes in the brain that lead to AD begin decades before symptoms appear, and since some of the known risk factors are particularly important during the midlife period, it is clear that reaching and engaging patients early, especially those who are at higher risk but not yet symptomatic, is essential. The goal of risk reduction should not be limited only to those with the highest risk, but we believe that those at higher-than-average risk are A) most likely to benefit, and B) most likely to comply with recommendations, and therefore we believe that coupling genetic risk testing with risk-reduction recommendations has substantial value.

ADx Healthcare's GenoRisk test offers patients and healthcare providers with a comprehensive approach to "Know Your Risk, Reduce Your Risk" for this devastating disease.

References

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