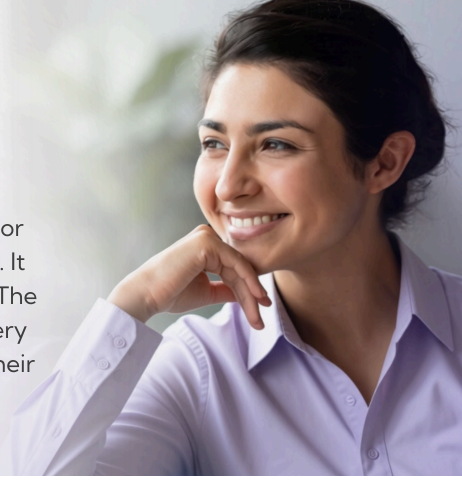
atlas™ PLUS

Technical Overview: *APOE* Add-On



This test uses *APOE* genotyping from whole-genome sequencing (WGS) to assess inherited risk for late-onset Alzheimer's disease, with genotype-associated cardiovascular and lipid considerations. It is offered exclusively as an add-on to Atlas Curated Screen* and cannot be ordered on its own.† The add-on uses the same genomic dataset generated by Curated Screen, which MyOme can re-query as healthcare needs change. Patients who have already completed Curated Screen can receive their *APOE* genotype through a re-requisition—no new sample required.

Clinical Use

This test determines *APOE* genotype (ε2, ε3, ε4)‖ in asymptomatic adults aged 18+ as one component of late-onset Alzheimer's disease risk assessment. *APOE* genotype is a risk factor, not a diagnosis: it cannot predict whether or when an individual will develop Alzheimer's disease.[1] Results may inform discussion of cardiovascular and lipid management[2], modifiable risk factors[3], amyloid-related imaging abnormalities (ARIA) risk stratification for anti-amyloid therapies[4], and implications for biological relatives, in conjunction with standard clinical assessment. Pre- and post-test genetic counseling is recommended when *APOE* testing is performed for Alzheimer's disease risk assessment.[1] Pre-test counseling is the responsibility of the ordering provider; MyOme offers post-test genetic counseling through a third-party partner, DNAvisit.

Method

Genomic DNA obtained from submitted samples is sequenced using Illumina technology, and reads are aligned to the human genome reference assembly GRCh38.p14. A high-coverage (mean 30x) PCR-free whole-genome library is constructed and sequenced to generate 2x150 bp paired-end reads. *APOE* genotype is determined by characterization of two common single-nucleotide variants, **rs429358** (c.388T>C, p.Cys130Arg) and **rs7412** (c.526C>T, p.Arg176Cys) on NM_000041.4; these correspond to legacy residue numbering p.Cys112Arg and p.Arg158Cys. The combination of alleles at these two positions defines the six reportable genotypes. Phasing is not resolved; because the ε1 allele is rare, individuals heterozygous at both positions are reported as ε2/ε4 rather than ε1/ε3. No orthogonal confirmation is performed.

Sample Types

- Blood (2 EDTA tubes)
- Buccal (2 swabs)

Turnaround Times

- Results are delivered in **~5–6 weeks** as a separate report alongside Curated Screen results.‡
- Re-requisitions for patients with previous Curated Screen results are typically completed in **~1 week**.

Test Performance[5]

PLUS (PR22057)

- 30x average genome-wide coverage
- >99.5% of exonic regions at ≥10x depth
- >99% sensitivity for SNVs and indels

*Formerly offered as "Single-Gene Risk" under MyOme Proactive Health. †*APOE* is reported separately from Curated Screen because ε4 is a common susceptibility allele rather than a pathogenic variant with established clinical management guidelines, and results are not orthogonally confirmed. ‡Turnaround times are provided as estimates and begin once sample(s) are processed at MyOme. Turnaround times may be extended in cases outside of MyOme's control. ‖This test characterizes only the two common *APOE* variants that define the ε2, ε3, and ε4 alleles; it does not analyze *APP*, *PSEN1*, or *PSEN2* (associated with autosomal dominant early-onset Alzheimer's disease) or polygenic contributions outside *APOE*.

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Included in Report

The report includes the *APOE* genotype and risk category (see table below), with genotype-specific interpretation covering Alzheimer's disease risk, cardiovascular and lipid effects, inheritance, and next steps.

Genotype	Population Frequency	Lifetime Alzheimer's Disease Risk[§]	Risk Category
ε2/ε2	<1%	Lower than average[6]	Decreased
ε2/ε3	~10–15%	Slightly lower than average	Decreased
ε3/ε3	~60% (most common)	Population baseline (~10–15%)[1,7]	Average
ε2/ε4	~2%	Slightly higher than average	Increased
ε3/ε4	~20–25%	~20–25% by age 85[8]	Increased
ε4/ε4	~2–3%	~50–60% by age 85[8]	Increased

§ Risk estimates and population frequencies reported here are derived primarily from studies of individuals of European ancestry. The magnitude of *APOE* ε4-associated Alzheimer's disease risk has been shown to vary across ancestral populations and may differ from the estimates presented in this report.[9]

1. Goldman JS, et al. Genetic counseling and testing for Alzheimer disease: joint practice guidelines of the American College of Medical Genetics and the National Society of Genetic Counselors. Genet Med. 2011;13(6):597-605. doi:10.1097/GIM.0b013e31821d69b8. 2. Mahley RW, et al. Pathogenesis of type III hyperlipoproteinemia (dysbetalipoproteinemia): questions, quandaries, and paradoxes. J Lipid Res. 1999;40(11):1933-1949. doi:10.1016/S0022-2275(20)32417-2. 3. Livingston G, et al. Dementia prevention, intervention, and care: 2020 report of the Lancet Commission. Lancet. 2020;396(10248):413-446. doi:10.1016/S0140-6736(20)30367-6. 4. Salloway S, et al. Amyloid-related imaging abnormalities in 2 phase 3 studies evaluating aducanumab in patients with early Alzheimer disease. JAMA Neurol. 2022;79(1):13-21. doi:10.1001/jamaneurol.2021.4161. 5. MyOme Inc. Data on file. 6. Reiman EM, et al. Exceptionally low likelihood of Alzheimer's dementia in *APOE2* homozygotes. Nat Commun. 2020;11:667. doi:10.1038/s41467-019-14279-8. 7. Liu CC, et al. Apolipoprotein E and Alzheimer disease: risk, mechanisms and therapy. Nat Rev Neurol. 2013;9(2):106-118. doi:10.1038/nrneurol.2012.263. 8. Genin E, et al. *APOE* and Alzheimer disease: a major gene with semi-dominant inheritance. Mol Psychiatry. 2011;16(9):903-907. doi:10.1038/mp.2011.52. 9. Rajabli F, et al. Ancestral origin of ApoE ε4 Alzheimer disease risk in Puerto Rican and African American populations. PLoS Genet. 2018;14(12):e1007791. doi:10.1371/journal.pgen.1007791.

This test was developed, and its performance characteristics determined, by MyOme, Inc., a clinical laboratory certified under the Clinical Laboratory Improvement Amendments of 1988 (CLIA) and College of American Pathologists (CAP) accredited to perform high-complexity clinical laboratory testing. This test has not been cleared or approved by the U.S. Food and Drug Administration (FDA). Test results should always be interpreted by a clinician in the context of clinical and familial data and with the availability of genetic counseling when appropriate.

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