Expert essay

Disclosing APOE genotype to individuals at risk for Alzheimer's disease

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Background

The link between the apolipoprotein E (APOE) gene on chromosome 19 and the risk of Alzheimer's disease dementia has been well-established for decades. Carriers of the e4 allele, who represent approximately a quarter of the general population, are at increased disease risk compared to the general population (where lifetime risk is approximately 10–15%), with e4 homozygotes presenting a particularly high risk (1). However, the e4 allele is neither necessary nor sufficient to cause Alzheimer's disease, and a recent pooled analysis of four large population-based cohort studies of older adults found that lifetime Alzheimer's disease risk in e4 homozygotes is less than 50%, a lower estimate than previous research had suggested (2).

Given its limitations in the predictive value and lack of proven Alzheimer's disease prevention options, APOE genotyping for susceptibility testing in asymptomatic individuals has generally been discouraged by medical experts. For example, a 2011 consensus statement from the American College of Medical Genetics and the National Society of Genetic Counselors recommended against APOE testing for predictive purposes in both clinical and direct-to-consumer (DTC) genetic testing contexts (3). Nevertheless, there is significant public interest in genetic susceptibility testing for Alzheimer's disease, particularly among those with a family history of the disease. Such individuals perceive numerous potential benefits from testing, including learning results that can inform advance planning (for example, purchasing insurance), decisions regarding medical care and clinical research, and engagement in health behaviours to reduce disease risk (4). In 2017, the DTC genetic testing company 23andMe obtained approval from the US Food & Drug Administration (FDA) to offer APOE testing for Alzheimer's disease risk assessment, which has provided millions of its customers the opportunity to learn their genotype.

APOE disclosure has also taken place as part of research studies of the psychological and behavioural impact of genetic susceptibility testing for Alzheimer's disease. Our REVEAL Study, a series of randomised trials examining APOE disclosure in populations at risk for Alzheimer's disease (for example, first-degree relatives), has demonstrated methods for successfully communicating genetic risk for Alzheimer's disease using processes that a) minimise risks such as a misunderstanding of results and clinically significant distress reactions, and b) require less time and human resources than traditional predictive genetic testing and counselling protocols for neurodegenerative diseases (such as Huntington's disease) (5).

> **Prior to undergoing APOE genotyping, individuals should be afforded the opportunity to learn about its potential benefits, risks, and limitations. They should know that testing will not provide them with a simple 'yes/no' answer about whether they will ultimately develop Alzheimer's disease dementia, and they should be mindful that results may have implications for other family members.**

Best practices in APOE disclosure

Our experience in disclosing APOE genotype status to over 1,000 individuals has yielded some key recommendations for healthcare professionals considering this practice.

1) Promote informed decision-making

Prior to undergoing APOE genotyping, individuals should be afforded the opportunity to learn about its potential benefits, risks, and limitations. They should know that testing will not provide them with a simple 'yes/no' answer about

whether they will ultimately develop Alzheimer's disease dementia, and they should be mindful that results may have implications for other family members; for example, all children of e4-homozygotes would necessarily be e4 carriers themselves. Concerns about genetic discrimination may be pertinent for some, with legal protections such as the US Genetic Information Non-discrimination Act (which covers health insurers and employers but not life, disability, or long-term care insurers) worthy of consideration. Such issues can be addressed in a variety of formats, including online decision aids (for example, www.genetestornot.org) that do not require involvement of genetic specialists (6).

2) Employ proven health communication techniques in disclosure

Ideally, knowledgeable healthcare professionals experienced in communicating sensitive health risk information should divulge results, with telephone and videoconferencing as acceptable alternatives to in-person disclosure. Given widely varying levels of health literacy and numeracy among laypersons, communication may need to be tailored to individuals receiving risk information (under the auspice that sometimes 'less is more'). Visual aids can enhance understanding of quantitative risk information, especially when comparing risk across different groups. In the REVEAL Study, we have used pictographs (Figure 1) to simultaneously demonstrate both absolute and relative risk associated with being an APOE4 carrier (7). Limitations of risk estimates should be conveyed. Individuals may possess risk or protective factors for Alzheimer's disease not accounted for in models generating risk estimates. In addition, the studies on which risk estimates are based often lack notable diversity in terms of race/ethnicity.

3) Provide guidance on appropriate next steps

APOE disclosure should be accompanied by recommendations for reducing disease risk. Although there are no proven means of preventing Alzheimer's disease, several health behaviours and interventions show promise in lowering the risk of Alzheimer's disease and related dementias, including regular physical activity and management of hypertension. The World Health Organization (WHO) summarised such approaches in its recently issued guidelines for risk reduction of cognitive decline and dementia (8). Individuals should also be made aware of substantive dementia education resources such as the Alzheimer's Association and the US National Institute on Aging. In addition, encouragement to participate in clinical Alzheimer's disease research may be appropriate

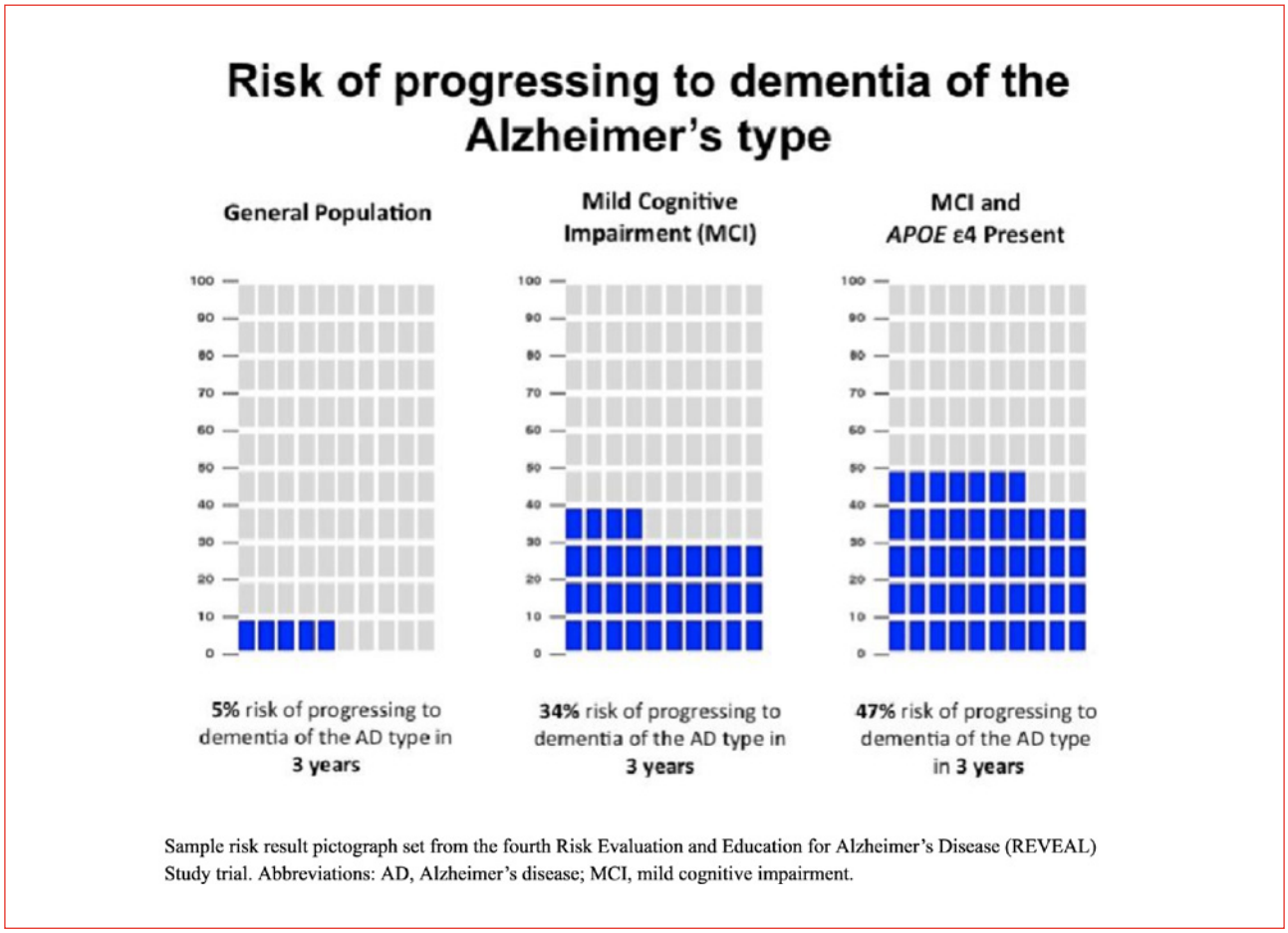

Figure 1. Reprinted from Lautenbach et al, 2013.

in some cases. All key information disclosed to individuals should be concisely summarised in a take-home document for future reference.

Emerging trends

APOE disclosure is increasingly being used or considered for purposes beyond merely informing interested individuals about their chances of developing Alzheimer's disease dementia. For example, APOE genotyping has been employed to help identify asymptomatic, elevated risk participants for Alzheimer's disease prevention drug trials (9). As noted elsewhere in this report (Chapter 24), APOE testing could assist in reducing costs of the Alzheimer's disease diagnostic process by helping determine which cognitively impaired individuals need (or don't need) expensive follow-up biomarker testing such as amyloid neuroimaging. The recent US FDA approval of aducanumab to treat Alzheimer's disease suggests a potential adjunctive role for APOE testing in informing medical decision-making, given that e4 carriers are at significantly elevated risk for the side effect of amyloid imaging related abnormalities (ARIA); APOE genotyping has already been used to inform clinical management of a e4-homozygote patient experiencing vasogenic oedema (ARIA-E) and intracerebral haemorrhage (ARIA-H) side effects from aducanumab use (10). These developments demonstrate the rapidly evolving uses and implications of APOE testing even three decades after its introduction.

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