CYTOX Defining Genetic Risk for Dementia

The clinical application of polygenic risk assessment to reduce the risk of cognitive decline in subjects with early cognitive concerns

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Introduction

While the recent FDA approval of Aduhelm (aducanumab) provides clinicians and patients with the first disease modifying drug for Alzheimer's disease, it may neither be available nor appropriate for all patients. Furthermore, this approval has spurred on many other drug development programmes with a similar mechanism of action – beta-amyloid removal – including gantenerumab from Roche, donanemab from Eli Lilly, and lecanemab from Biogen and Eisai. To date, these products have successfully caused a depletion of beta-amyloid in the brain. However, on approval of Aduhelm, the FDA requested that further studies are conducted to confirm the clinical benefits, not just proof of reduction in beta-amyloid since this was not fully established in Biogen's Phase 3 trials. As such, while there is much optimism for new therapeutic interventions coming through, it is evident that wide-scale adoption is still some years away.

Fortunately, there is mounting evidence that lifestyle interventions and behavioural changes play a significant role in maintaining cognition and function, as well as preventing or delaying the onset of disease[1]. Indeed, with modifiable factors accounting for more than 40% of the risk for dementia, it is important that clinicians confronted with patients with early cognitive concerns, have appropriate tools available to assist in diagnosis and the understanding of future risk of progression so as to provide appropriate clinical management. The application of polygenic risk score (PRS) tests has the potential to contribute towards management planning and to reduce the burden of testing in patients with low overall risk. This white paper aims to provide an overview of the potential role of PRS testing and how it may be applied to identify those individuals at highest risk of cognitive decline due to Alzheimer's disease, and guide and support clinical management decisions for those high risk individuals of developing Alzheimer's disease (AD).

The genetics of Alzheimer's disease: what is polygenic risk and how may it be determined?

Alzheimer's disease is the most common form of dementia and the genetics of Alzheimer's is the best understood of all the common dementias[2]. It has been shown that AD appears in families and that there can be both simple (single-gene mutation) and complex (multigene variant) inheritance patterns, with the genes involved in each kind of inheritance being different. The identification of the first genes involved in AD arose from family-based studies, but risk factors have mainly been identified by studies comparing groups of patients with age-matched control groups[3]. So-called linkage analyses performed in the early 1990s identified the only fully penetrant mutations known to date to be involved in this disease. Familial Alzheimer's disease, also termed early-onset AD (EOAD), is rare and has been reported in around 600 families worldwide, in which close family members are affected by AD across successive generations. Furthermore, people with one of these extremely rare mutations tend to develop Alzheimer's disease early, in their 30s, 40s or 50s. Studies of the affected families show that their AD is usually caused by a mutation in one of just three genes; amyloid precursor protein (APP) and two presenilin genes (PSEN-1 and PSEN-2), with more than 450 known families worldwide carrying a mutation in the PSEN-1 gene on chromosome 14 and thus causing up to 80 per cent of all familial AD. When all AD, irrespective of age of onset is considered, fewer than 1 in 100 cases are thought to be caused by mutations in these three genes.

The vast majority of people with Alzheimer's disease do not inherit it from a parent as a single-gene mutation with a simple inheritance pattern. Instead, the inheritance follows a more complex genetic pattern. The disease might skip a generation, affect people on both sides of the family, appear seemingly from nowhere or not be passed on at all.
More than 20 gene variants (or regions within the DNA) have now been identified which impact upon the risk of an individual developing AD[4]. The effects of each of these gene variants is subtle, but variants act to slightly increase or decrease the risk of a person developing Alzheimer's disease. These so-called 'risk genes' or DNA sequence variants, interact with each other and with other factors, such as age and lifestyle, to influence someone's overall risk of getting the disease[2]. The most influential single genetic risk factor for sporadic or late-onset AD (LOAD) was identified as the E4 allele of APOE (Apolipoprotein E) and importantly, this was found to increase the risk for Alzheimer's disease in different sporadic populations. There is considerable research interest in understanding whether the APOE-ε4 allele (variant) influences cognition in healthy adults. Despite a substantial literature reporting effects of APOE genotype on cognition, the findings are inconsistent. In particular, it is challenging to separate whether cognitive deficits in APOE-ε4 carriers reflect the influence of prodromal dementia pathology ("prodromal hypothesis"), or a direct contribution of APOE genotype to individual differences ("phenotype hypothesis")[5].

The role of PRS tests in changing behaviour & modifying lifestyle factors to mitigate risk of AD

To drive lasting behavioural change, an individual must understand their genetic risk for AD, alongside other known risk factors, and be to provided with actionable steps to offset those risks.

In 2015, the American College of Medical Genetics and Genomics (ACMG) defined clinical utility of genetics and genomics services. Clinical utility occurs when "...diagnoses of genetic diseases that are medically actionable with clear benefit to patient outcomes..."[7]. The ACMG concluded that in order to maximize the potential of DNA-related risks to change behaviours, these factors needed to be addressed:

- The information needs to be understood by the patient
- The information has to be meaningful to the patient
- The information has to be actionable
- The information should be reinforced

What role can polygenic risk play in clinical management of Alzheimer's disease and dementia?

A polygenic risk score, also called a genetic risk score, or genome-wide score, is a number based on variation in multiple genetic loci and their associated weights. It serves as the best prediction for the trait that can be made when taking into account variation in multiple genetic loci[6,7,8]. Tests to triage people at high genetic risk of developing late-onset Alzheimer's disease (LOAD) will be of the utmost value as soon as a disease modifying therapy is available, but these are also extremely important for current drug development and clinical practice today. Even in the absence of a disease modifying drug, an inexpensive and easily accessible test to enable the identification of individuals at risk or with pre-clinical AD would be of enormous value. There is robust and increasing evidence that a variety of lifestyle interventions and behavioural changes can play a significant role in maintaining cognition and function, as well as preventing or delaying dementia[1], with modifiable factors accounting for more than 40% of the risk for dementia. Randomised clinical trial evidence has suggested that straightforward interventions such as physical exercise[9], cognitive training[10,11] and multi-faceted interventions combining lifestyle elements[12] confer significant benefits in maintaining cognition and function in mid and later life. Importantly, engagement with these interventions in the context of clinical trials has been good, giving potential to expand these as public health interventions – especially those elements such as cognitive training which have been effectively delivered using digital platforms[11].

One such study designed to test the impact of lifestyle changes is the so-called FINGER study led by Professor Miia Kivipelto and colleagues[13]. This was established in order to test the potential benefits of longer-term interventions (2 years) on cognitive impairment. The Finnish Geriatric Intervention Study to Prevent Cognitive Impairment and Disability study (FINGER) investigated the effects of a 2-year intervention targeting several lifestyle and vascular risk factors simultaneously. FINGER is the first multi-domain lifestyle intervention programme that has shown that a combination of lifestyle interventions is able to prevent or slow down cognitive decline and thereby provides the

basis of a powerful incentive for those deemed to be a high genetic risk for LOAD to adopt proactive lifestyle changes in individuals who are either currently cognitively normal or experience very early subjective memory complaints[13,14]. Not all attempts to demonstrate positive benefits of such interventions have been successful, but even in studies such as MAPT and Pre-DIVA where formal study end-points were not met, trends were still evident[15] Building on the success of FINGER, a new randomised-control trial called MIND-AD has now begun in Europe to adapt the FINGER protocol to people who already have mild Alzheimer's disease[16]]. (Figure 1).

Taking Control of Brain Health

For individuals with cognitive complaints or concerns there is a new genetic test, only available through a physician, which can provide insight into the risk off developing Alzheimer's disease in the future. With this knowledge an individual can discuss, with their physician, the actions that can be taken to mitigate the risks of the onset and development of Alzheimer's disease symptoms

Figure 1: Taking control of brain health

An opportunity to change behaviour and reduce future risk?

Understanding genetic risk for LOAD, together with exposure to other known risk factors combined with proven, actionable steps that can be taken by an individual, is crucial to drive lasting behavioural change. There are several studies which have looked at the impact of communicating genetic risk of disease on risk-reducing behaviour and many of these have concluded that communicating DNA based disease risk estimates has little or no effect on risk-reducing health behaviour in isolation[17]. However in 2015, the American College of Medical Genetics and Genomics (ACMG) published a position statement on how to define clinical utility of genetics and genomics services. Clinical utility occurs when *"...diagnoses of genetic diseases that are medically actionable with clear benefit to patient outcomes..."* [18]. Specifically, it was concluded that in order to maximize the potential of DNA-related risks to change behaviours, other factors needed to be addressed:

- The information needs to be understood by the patient
- The information has to be meaningful to the patient
- The information has to be actionable
- The information should be reinforced

Quality healthcare outcomes depend upon patients' adherence to recommended treatment regimens. In some disease conditions, more than 40% of patients sustain significant risks by misunderstanding, forgetting, or ignoring healthcare advice. While no single intervention strategy can improve the adherence of all patients, decades of research studies agree that successful attempts to improve patient adherence depend upon a set of key factors. Physician–patient partnerships are essential when choosing amongst various therapeutic options to maximize adherence and for this reason it is proposed that PRS testing and reporting, is most appropriately administered by a physician or suitable healthcare professional.

The application of *geno*SCORE to understanding genetic risk for LOAD

*geno*SCORE-LAB, in Europe, and the IBX Alzheimer's Risk Test in the US and Canada are examples of a newly-available approved tests that may be used to assess genetic risk for the future development of Late-Onset Alzheimer's disease (LOAD) as derived from a Polygenic Risk Score (PRS) calculation. Based on work pioneered at Cardiff University[19], these tests, both powered by the Cytox *geno*SCORE™ technology, are the only physician use PRS tests available to date. The *geno*SCORE powered tests have been validated in a data set of exclusively pathologically confirmed AD cases alongside autopsy confirmation of AD, which is the gold standard. In its analysis, *geno*SCORE showed more accuracy in disease prediction in pathologically confirmed cases than in other validation sets without explicit autopsy confirmation[20]. Furthermore, this test has been demonstrated to predict individuals at greatest risk of further progression of cognitive impairment due to Alzheimer's disease in individuals from the so-called ADNI data set using a polygenic risk scoring algorithm. This risk of cognitive decline, as measured using either the ADAS-Cog13 points, CDR-SB and PACC rating scales, showed significant declines in the scores over 4 years, in higher risk individuals compared with almost no change in the lower risk group[21]. Additionally, a clear relationship was demonstrated between *geno*SCORE and the pTau/Aβ1-42 ratio in cerebrospinal fluid (CSF), with the vast majority of individuals who have a pTau/Aβ1-42 ratio of >0.028 having a high *geno*SCORE. The pTau/Aβ1-42 ratio in CSF is considered a gold standard measure for assessing risk of decline due to AD, but such testing presents significant operational challenges to perform routinely[22].

Individuals with a high *geno*SCORE test result are therefore likely to be at increased risk of cognitive decline associated with LOAD. *geno*SCORE tests require a mouth swab or blood sample and are very convenient and simple to use, allowing elderly and vulnerable patients to provide a sample from home if self-isolating due to COVID-19, or not wishing or easily able to attend a healthcare setting. *geno*SCORE tests provide an analysis of over 100,000 common genetic variations that are risk-associated with, or protective against, the development of AD.

*geno*SCORE test in clinical practise

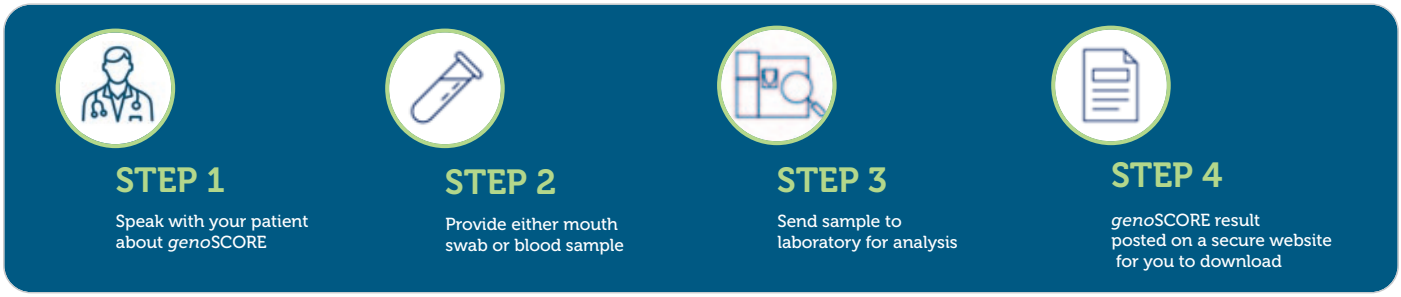

Figure 2: *geno*SCORE test work-flow for physicians

Risk classification is assigned by comparing the *geno*SCORE result to the distribution of scores obtained from an age-matched general population (using data from 1000 genomes project). Lower risk is defined as the bottom quartile of that distribution, typical risk as the middle 50% of that distribution and higher risk as the top quartile of that distribution. The *geno*SCORE result includes age as a co-variate and will increase with time to reflect the additional risk of onset of LOAD that comes with increasing age. Also reported is the patient's relative risk against the general population for that specific age, expressed as a percentile. This score remains constant (Figure 3a and 3b). Known age related prevalence (Alzheimer's Association Report 2020) provides further context in understanding absolute risk as well as relative risk.

*geno*SCORE heat-map

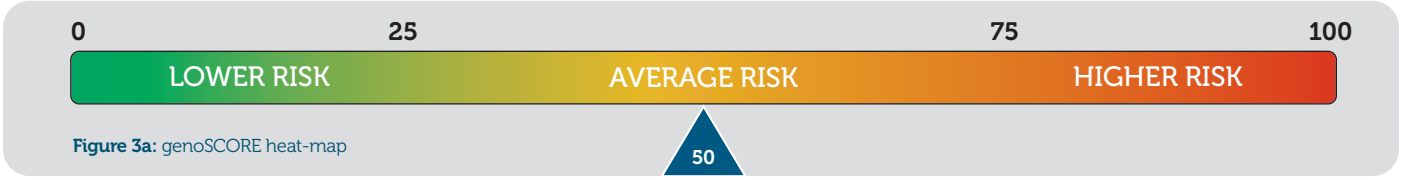

Figure 3a: genoSCORE heat-map

*geno*SCORE report details and APOE status

Age	65
*geno*SCORE	0.58
*geno*SCORE percentile	50*
APOE status	E3/E3

*In a general population of 100 people of your age and sex, 50 have a higher *geno*SCORE than you, 49 have a lower *geno*SCORE than you.

Figure 3b: genoSCORE report details and APOE status

A high *geno*SCORE test result does not indicate that an individual will definitively develop LOAD in the future, and conversely a low *geno*SCORE result does not categorically mean that subsequent onset of LOAD will never occur. The test result should be used in conjunction with other information available to the physician.

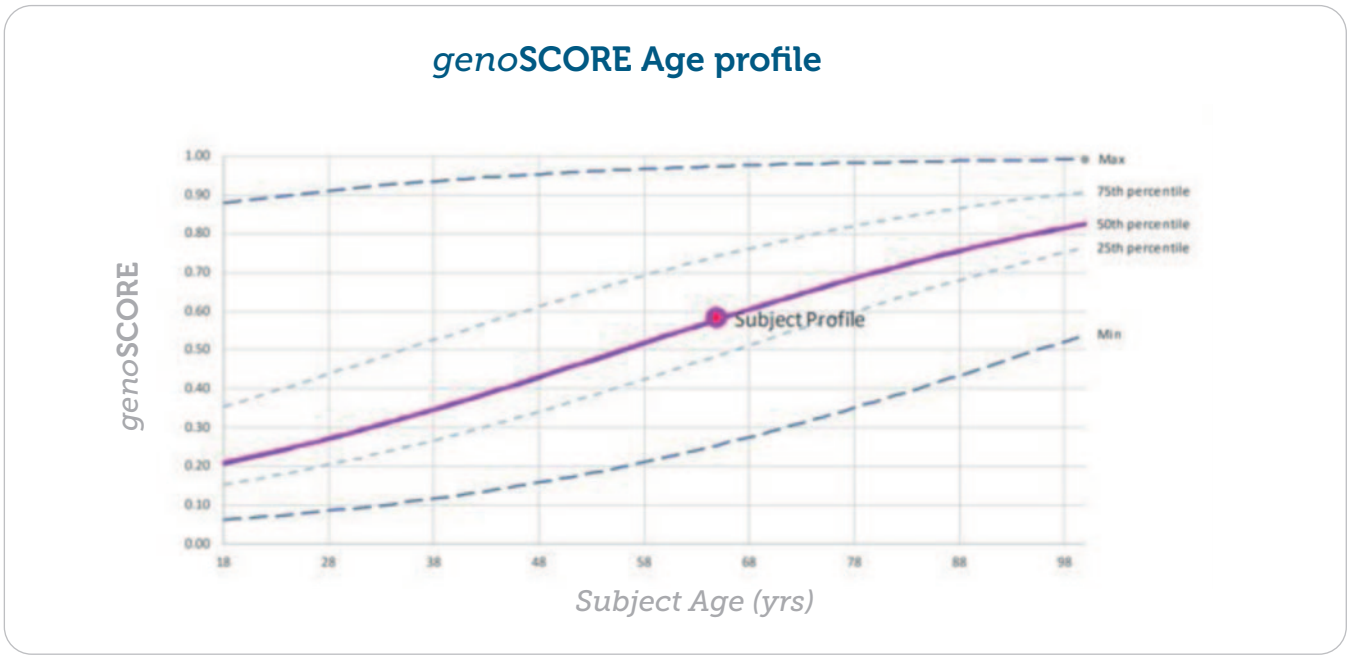

Figure 3c: *geno*SCORE age profile

A glimpse of the future?

The *geno*SCORE powered tests are able to provide a valuable assessment of genetic risk of individuals most likely to decline cognitively decline towards AD and as such, has the potential to contribute significantly to clinical management decisions. The ease and effectiveness of home sampling of saliva as source DNA for *geno*SCORE tests is a major consideration and well aligned with the continuing need for remote consultations in the light of the COVID-19 pandemic. Further larger-scale studies to determine the full clinical and associated economic impact of the *geno*SCORE tests will be required.

Concerns have been raised about the potential impact of disclosing AD risk information to individuals. However, previous research, notably in the form of the REVEAL studies, have explored the possible behavioural and psychological impacts of receiving genetic risk information for Alzheimer's disease (AD). These important studies have shown that such genetic risk information can be given to individuals in a variety of ways and further, that it will be well understood and with minimal risk of significant short-term psychological risks[23]. Nonetheless, caution will be needed in setting expectations and managing communication of complex genetic risk data[24]. Further work will certainly be needed to extend the application of PRS testing across different disease areas and with an emphasis upon extending the application beyond the mostly Caucasian ethnic groups for which most are applicable, a situation which has arisen due to the predominance of sample availability in large GWAS datasets[25,26].

The evidence in support of the clinical utility of PRS approaches to the improved diagnosis, prognosis and clinical management of LOAD is compelling. This approach offers the potential to identify higher risk individuals very early and to encourage the adoption of preventative measures to mitigate the ultimate risk of developing the disease. It is notable that a number of major insurers and health providers are now beginning to implement these approaches proactively to millions of individuals, particularly in the US. Smoking, a key known risk factor for dementia, has also been shown to be modifiable at a population level and other key medical risk factors such as hypertension and depression[1] are amendable to effective intervention. Very importantly, recent evidence highlights that the potential for modification of medical and lifestyle risk factors to modify dementia risk is not diminished even amongst the individuals at highest genetic risk[27]. With the relative ease of access, affordability and actionable outcomes, it is anticipated that PRS testing and preventative approaches, will become an important component of managing dementia risk.

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