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# Genetic risk assessment in Alzheimer's disease

To date, the diagnosis of Alzheimer's disease has largely focused on clinical symptoms. Current tests include positron emission tomography (PET) and magnetic resonance imaging (MRI) to observe physical changes in the brain and cerebrospinal fluid (CSF) analysis to identify biomarkers associated with the disease. It is also possible to test for the presence of variants of the APOE gene, one of which is known to increase an individual's risk for developing late-onset Alzheimer's disease.

In this article I discuss a fourth option which is being explored by our company Cytox Ltd in the UK. This is to assess a person's genetic risk for Alzheimer's disease by using a technique called polygenic risk scoring.

The context is the realisation by many scientists that the current methods for diagnosing Alzheimer's disease have shortcomings. PET scanning enables healthcare professionals to observe the deposition of amyloid plaques in the brain, a hallmark of Alzheimer's. However many patients with plaques show no cognitive impairment. MRI scanning can reveal changes in the physical structure of the brain, including the loss of brain mass. However these changes do not necessarily result in Alzheimer's or cognitive decline. CSF analysis detects biomarkers associated with the disease such as amyloid-beta and tau. But, as with the scanning techniques, the presence of these biomarkers has some correlation with disease and symptoms but can also be present in patients who do not develop the disease.

Testing for APOE genetic variants can offer greater insight into the risk of developing Alzheimer's. Indeed, the e4 version of the APOE gene is recognised as the single most significant genetic risk factor for future development of late onset disease. However, while 20-30% of humans are APOE e4 carriers, these individuals only account for up to 60% of all Alzheimer's cases. At least 40% of Alzheimer's patients do not carry APOE e4[1].

While all of the current approaches are valuable tools in the diagnosis of Alzheimer's, none can provide either a definitive assessment of risk or any predictions of the timing of disease onset. Why is this important? First, early risk assessment would enable timely interventions, such as changes to a person's lifestyle. Second, being able to estimate disease onset would improve recruitment of patients to clinical trials for new drugs, as well as the development of companion diagnostics for these drugs.

The polygenic risk scoring test being developed by Cytox is non-invasive and designed to assess the probability of Alzheimer's arising, based on multiple genetic loci and their associated disease-causing weights. The technique is not unique to Alzheimer's, indeed there is substantial research underway on polygenic risk scoring approaches in coronary artery disease, Type 2 diabetes, inflammatory bowel disease, breast cancer and glaucoma.

The Cytox approach for Alzheimer's disease is to calculate a polygenic risk score on the basis of two components. First, there is an array that contains around 800,000 probes to detect around 500,000 single nucleotide polymorphisms (SNPs) linked to Alzheimer's - these SNPs may be either causative of, or protective against, the disease. To interpret the output from the array, and calculate the final polygenic risk score for any individual, the company uses artificial intelligence-derived algorithms and proprietary interpretive software.

The content on the array has been curated from a number of sources including the International Genomics of Alzheimer's Project dataset, widely regarded as the gold standard; genome wide association studies; a comprehensive review of the literature and in-house studies. Cytox has been working with the Cardiff University in the UK to take its leading polygenic risk score algorithm and develop it for assessing the risk of the future onset of Alzheimer's disease.

In addition, the company has been collaborating with the

### Public views on diagnosing Alzheimer's disease

It's a common medical dilemma – if there's little therapy available, do patients want to know if they have a disease and will become ill? Alzheimer's disease raises exactly this dilemma, assuming that we will one day be able to assess the risk of the disease developing, potentially decades before symptoms ever present.

A recent UK report from Alzheimer's Research UK, and Merck & Co Inc, explored public attitudes towards diagnostics for Alzheimer's disease[1]. The report was based on two data sets, first a series of focus groups, and then a more extensive survey of 2,106 adults in the UK, approximately half with experience of dementia through a family member, friend, or being a carer; the remainder with no personal connection to dementia.

Commenting on the discussions within the focus groups, the report noted: "The most common spontaneous response...was that tests should be used when symptoms start to appear." However, the discussion lead to many questions along the lines of: "Can I change my outcome or level of risk?" and "How can I reduce my risk?"

The report noted: "On the whole, the focus group discussion indicated stronger support for early detection when people had more certainty about their level of risk. This can help people to gain control over their situation, either as patients, carers or family members."

The survey results were very clear: 74% of people said they would want to know if they had Alzheimer's disease before symptoms develop. This breaks down to 38% who would want to know 15 years ahead of symptoms, and 33% two years ahead of symptoms.

Reference: www.alzheimersresearchuk.org/wp-content/uploads/2019/12/1132267-Public-Perceptions-Report_v5.pdf

 

University of Birmingham in the UK to unlock the power of polygenic risk scoring algorithms and provide more information around the contribution of underlying molecular pathways associated with disease. While, as previously discussed, APOE e4 contributes significantly to genetic risk, it quite clearly does not account for all the risk attributed to the genetics. It is only through understanding the aggregate influence of the wide range of SNPs that you can attain a comprehensive picture of genetic risk for Alzheimer's disease.

## How the landscape is changing

Alzheimer's disease has been, and remains, an extremely challenging disease to tackle. The last 15 years have seen a catalogue of disappointing clinical trial failures for therapies looking not just to alleviate symptoms but to modify the underlying disease. The most recent of these failures were reported by Eli Lilly and Company and Roche on 10 February in the rare, inherited form of autosomal dominant Alzheimer's disease.

However, recent news that Biogen Inc and Eisai Co Ltd are planning to seek US Food and Drug Administration approval of their anti-amyloid drug aducanumab has provided new hope to the field. The past decade has been dominated by amyloid-beta as the primary drug target being pursued by most pharma companies. Now a number of new mechanisms are being explored such as tau and inflammatory pathways.

The amyloid precursor protein and the tau protein represent the most abundant and important proteins in the central nervous system. However, when the pathways associated with their normal function go wrong it leads to the deposition of misfolded versions of the protein which leads to plaques and tangles in the brain with an assumed impact on healthy brain tissue. By targeting drugs to these misfolded proteins it is hoped that plaques and tangles can be cleared from the brain and with a subsequent positive impact on cognitive performance. Inflammation in the brain is also thought to be a key process in the progression of Alzheimer's disease by causing cell death.

During this period of drug development, the need for accompanying diagnostic and biomarker tests has intensified. This has driven more recent efforts to focus on developing blood tests for amyloid and tau biomarkers, as these reduce the cost and invasiveness of testing. However, these new tests still fall short of assessing risk of disease, and the timing of onset.

Moving beyond these, the underlying basis of Cytox's test is to understand the risk of any individual towards future onset of disease and in principle can be taken at any point in time. However, the near-term opportunity is to use genetic risk assessment to stratify individuals for further clinical trials that will detect the presence of Alzheimer's related pathologies.

*Reference*

1. JAMA (1997) **278**, 1349 Farrer et al.

This article was written by Dr Alex Gibson, Business Development Officer at Cytox Ltd.