Validation of a novel blood test for the early detection of Alzheimer’s disease – challenges with an 'imperfect gold standard'

Birgitte B. Booij, Phil D. Rye, Gisle Grave, Hilde-Marie Andersen, Lena Kristiansen, Marianne Jensen, Ken Bårdsen, Torbjørn Lindahl, Praveen Sharma, Anders Lönneborg.

DiaGenic ASA, Grenseveien 92, NO-0663 Oslo, Norway

Objectives and study:
Early and accurate detection of Alzheimer’s disease (AD) is critical for implementing active management strategies which may delay the onset of the more debilitating symptoms of AD. Our objective was to develop a blood test (ADtect®) that can be used to aid the early diagnosis of AD.

Methods:
Our unique approach detects the presence of disease by measuring the pattern of specific gene expression changes in peripheral blood. This is a novel diagnostic approach as it measures the systemic effects of the disease. The test requires a 2.5 mL venous blood sample collected in an FDA approved PAXgene tube, which stabilizes and preserves the RNA. The RNA is then extracted and cDNA prepared before application to a low density array (ADtect®). The performance of all the 96 gene assays in the real-time RT-PCR analysis is evaluated by an algorithm that results in a test score value indicating the presence or absence of AD.

Results:
In a multicenter study of N=248 subjects the test is able to discriminate AD subjects from cognitively healthy controls with a 73% overall agreement with the clinical diagnosis. The test performance is confirmed in an independent validation study, and shows similar good performance in mild (MMSE 20-27) and moderate AD cases.

Conclusion:
We have developed a blood test (ADtect®) that can be used to aid the early diagnosis of AD. Our current findings show that ADtect® is a reliable and diagnostically relevant biomarker for the early detection of AD. Assuming a clinical accuracy of 80% in a validation study, a biomarker with 90% “true” accuracy can be expected to give an observed accuracy of 70-75%. The ADtect® blood test is particularly valuable as an aid in the diagnosis of mild AD cases with minor cognitive decline which are clinically the most difficult cases to diagnose.