Developing a Saliva-based Polygenic Risk Scoring Test for Effective Stratification of Potential Alzheimer's Disease Related Clinical Trial Participants

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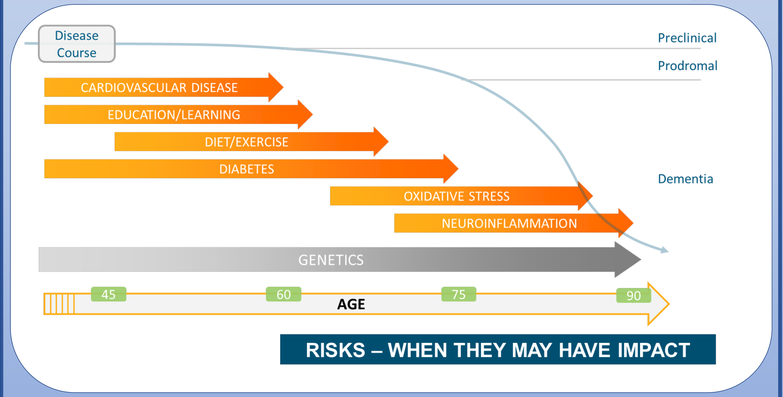
Key Conclusions

Using DNA easily accessible from saliva, can provide a more efficient manner for identifying participants most likely to decline cognitively and therefore enriching clinical trials with more suitable patients. Using PRS algorithms prior to more invasive, expensive or burdensome procedures provides a strategy to screen out unsuitable patients very early in the recruitment process. Importantly this also provides clinicians with more information of future risk of disease progression enabling better management decisions for patients with very mild cognitive symptoms.

Background

- The development of diagnostic tools to identify disease risk is critical to enable selection of suitable individuals for inclusion into clinical trials and cohort studies. The utility of Polygenic Risk Scores (PRS) is gaining increasing attention for generating an individual genetic risk profile and subsequent estimation of future disease risk in Alzheimer's Disease. Cytox has developed a streamlined integrated process called *geno*SCORE™, taking DNA from either a blood or saliva sample, through genotyping and PRS calculation to produce an estimation of risk of Alzheimer's Disease.

- Patients who present to clinicians with very mild or subjective cognitive complaints can provide a diagnostic and patient management challenge in terms of decisions on whether to progress to more expensive and/or invasive testing or to discharge. Easy access to access risk evaluation data will help better patient management decisions in a cost-efficient manner and provide further basis for dialogue on risk mitigation through lifestyle changes



Underlying genetic risk coupled with age and environmental risks

Objectives and Methods

- To demonstrate the ability to predict individuals at greatest risk of further progression of cognitive impairment due to Alzheimer's disease in individuals from the ADNI using a polygenic risk scoring algorithm.
- To compare the performance of the algorithm in predicting cognitive decline against that of using the pTau/Aβ1-42 ratio.
- 290 individuals, where suitable genetic data was available together with at least 4 years' worth of longitudinal cognitive testing and baseline CSF measurements, were included in the analysis.
- A proprietary software, called SNPfitR™ was developed by and used to calculate a '*geno*SCORE' (polygenic risk score) for all individuals. This calculation is based on a significantly modified algorithm originally published by Escott-Price *et al* and includes age, sex and presence of both APOE4 and APOE2 as covariates. A threshold of 0.6 designated as either at higher or lower risk.
- The predictive accuracy of the PRS algorithm in determining longitudinal changes in cognitive performance, as measured by ADAS-Cog13 and CDR-SB for up to 4 years was then tested. Furthermore the relationship of CSF biomarker status with *geno*SCORE was established

Number	**290**
Age mean (SD)	72.3 (7.3)
Male/Female	179/111
CDR-SB at baseline mean (SD)	14.6 (6.3)
CDR-SB at year 4 mean (SD)	19.7 (14.4)
PRS positive (>0.6)	196
PRS negative (<0.6)	94

Table 1 – Characteristics for participants

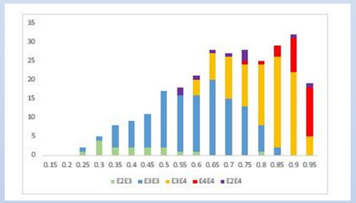


Figure 1 – Distribution of risks scores across the MCI population coloured by APOE genotype

[1] Escott-Price V, Sims R, Williams J et al, Common polygenic variation enhances risk prediction for Alzheimer's disease. Brain 2015;138;3673-3684
[2] Hansson O, Seibyl J, Stomrud et al, CSF biomarkers of Alzheimer's disease concord with amyloid-β PET and predict clinical progression: A study of fully automated immunoassays in BioFINDER and ADNI cohorts. Alzhemers Dement 2018;14;1470-1481.
[3] Daunt P, et al, Polygenic risk scoring is an effective approach to predict those individuals most likely to decline cognitively due to Alzheimer's disease. *J Prev. Alz. Dis.* 2021; 1(8), 78-83

Results and Discussion

- Figure 2 clearly demonstrates a clear relationship *geno*SCORE and pTau/Aβ1-42 ratio with the vast majority of individuals who have a pTau/Aβ1-42 ratio of >0.028[2] having a high *geno*SCORE. Furthermore, those individuals with both a high *genoSCORE and high* pTau/Aβ1-42 ratio are those most likely to decline cognitively .
- The accuracy as measured by area under the curve (AUC) for predicting individuals who declined at least 10 ADAS-Cog13 points over 4 years from an MCI baseline was 74% (Figure 3).

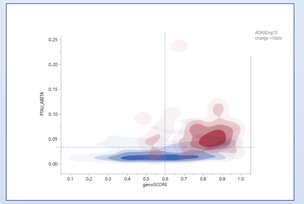


***Figure 2 – Density Plot showing relationship between* genoSCORE, pTau/Aβ1-42 ratio and cognitive decline over 4 years**

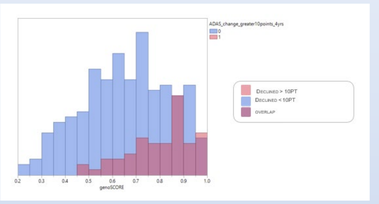


Figure 3 – genoSCORE distribution of MCI individuals showing a propensity for high risk individuals to decline by at least 10 ADAS-Cog13 points at 4 years

- Using a *geno*SCORE threshold of 0.6, a higher risk (n=196) and lower risk group (n=94) were identified and the average CDR-SB score for each group plotted over 4 years. Figure 4 shows that the high risk group on average declined, on average, by 2 CDR-SB scores over 4 years compared with almost no change in the low risk group. When considering APOE3 homozygtoes only high risk *geno*SCORE individuals still declined more than their low risk peers.
- Further analysis of this data can be found in Daunt *et al*[3]

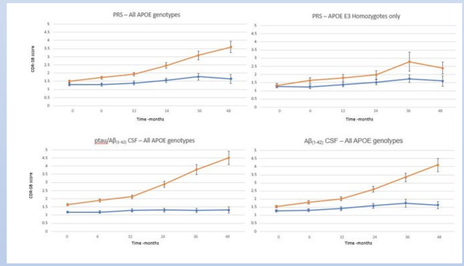
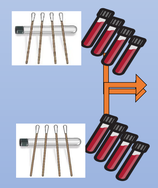


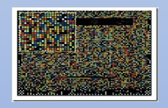
Figure 4- Time course of clinical progression in patients with MCI over 48 months. Average with standard errors by group (orange >0.6; blue <0.6 at baseline) for all APOE genotypes and for APOE homozygotes only, pTau/Aβ(1-42) group (orange > 0.028; blue <0.028) and Aβ(1-42) (orange < 880pg/mL; blue >880pg/mL)

genoSCORE-LAB

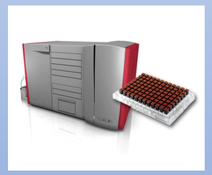
The SNPfitR™ analysis package and Cytox integrated platform offers fast, accurate, reliable and cost-effective genetic testing solution from whole blood or saliva to assess Alzheimer's Disease risk



Input from extracted DNA, blood or saliva

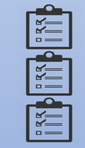


Custom Cytox variaTECTII™ array



Genotyping on Applied Biosystems GeneTitan™ MC Instruments.

Proprietary SNPfitR™ pipelines for automated analysis



*Output reports with polygenic risk score, APOE status & flagging presence of SNPs associated with EOAD**

* The assay has not been fully validated for detection of EOAD SNPs so it is recommended that specific testing should follow to confirm the presence of any such SNPs