Clinical Experience with Polygenic Risk Score in Subjects with Early Cognitive Concerns

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CYTOX
Defining Genetic Risk for Dementia

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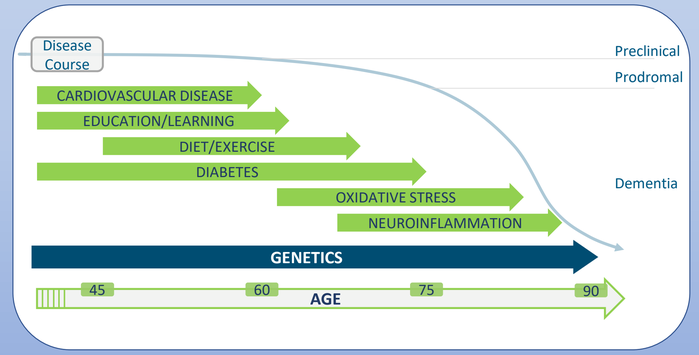
Key Conclusions

In this case study, the *geno*SCORE PRS test provided a valuable assessment of genetic risk for this individual who was concerned about his likelihood to decline cognitively decline towards AD and as such, contributed significantly to his personal action plan. The ease and effectiveness of home sampling of saliva as source DNA for the PRS test was considered greatly beneficial and well aligned with the continuing need for remote consultations in the light of COVID-19 concerns. Further larger-scale studies to determine the full clinical and associated economic impact of the *geno*SCORE PRS test are required.

Acknowledgements: We would like to thank the patient who provided candid feedback of their full experience

Background

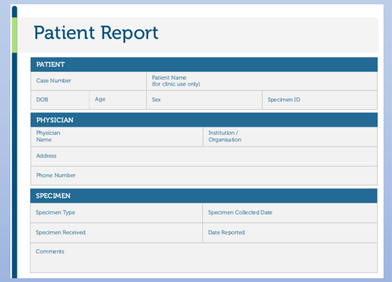
- Patients who present to clinicians with very mild or subjective cognitive complaints can provide a diagnostic and patient management challenge in terms of decisions on whether to progress to more expensive and/or invasive testing or to discharge. Easy access to access risk evaluation data will help better patient management decisions in a cost-efficient manner and provide further basis for dialogue on risk mitigation through lifestyle changes.
- Furthermore the very recent FDA approval of aducanumab is inevitably going to increase the demand from patients to access new treatment. Effective ways of stratifying patients is going to be required in order to meet this challenge
- Patients, with many different perspectives, are increasingly wishing to understand their risk of future disease. Understanding genetic risk will provide context and motivation for patients to take lifestyle interventions to mitigate against such risk.

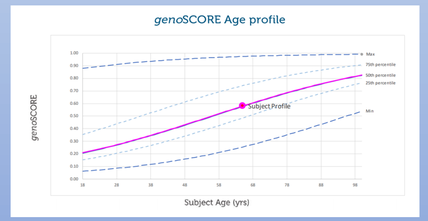


Underlying genetic risk coupled with age and environmental risks

Objectives and Methods

- *geno*SCORE-LAB was recently launched in EU as a CE-marked test and early anonymised user experience sought as part of understanding:
  - *The motivation for individuals to pay for an Alzheimer's genetic risk test in the context of a clinician led consultation*
  - *The impact on the patient on receiving the results*
- Here we present the experience from a 76 year old healthy male who:
  - Is highly educated and still active in various business activities
  - Had a strong family history (father and elder brother) of dementia but experienced no symptoms himself
  - Wanted to confirm his own suspicions that he was not in 'high risk 'category.
- Following a clinical consultation where family history and personal history were discussed together with pre-test counselling the patient provided a saliva sample for testing.
- Upon completion of the analysis a report was provided to the clinician for subsequent discussion with the patient (an example of elements of the patient report are shown below.
- Report elements include:
  - The polygenic risk score or *geno*SCORE on a scale between 0 and 1 – including age, sex and APOE as co-variates
  - Patient's relative risk as a percentile of scores generated from an age matched general population
  - APOE genotype
  - Age related profile showing how *geno*SCORE increases with age
  - Flags to show the possible presence of any SNPs (APP or PS1/2 related) associated with early onset Alzheimer's disease (note any positive findings should be confirmed in further genetic test)





Results and Discussion

Patient Results

- Sampling process very straightforward.
- PRS placed individual on the 50th percentile for his age and thus considered of average risk.
- APOE E3E3 genotype.
- As expected in 76y old patient no EOAD SNPs flagged

Patient Reaction

- Pleased to carry no EOAD mutations and not identified as having high genetic risk for onset of AD (though slightly disappointed not to be low risk)
- Age related risk profile does require explanation by physician in the context of increasing risk of AD with age
- Had thoroughly thought through consequences of knowing result by considering actions that could be taken if identified as high risk
  - Reduce business activities to focus only on commitments that he most enjoys
  - Spend more time with family
  - Organise personal affairs
  - Adopt an even more energetic lifestyle

Considerations for using Polygenic Risk Stratification in Clinical Practice

- Preventing or delaying Alzheimer disease where possible must be the priority. Understanding personal risk for future onset of Alzheimer's disease can be a great motivator for many to make suitable lifestyle interventions to reduce risk.
- Even more patients are likely to present to their doctors about brain health concerns following approval of Aducanumab – how can these patients be appropriately managed to allay concerns or move forward in the patent management path
- Comprehensive genetic risk stratification provides an opportunity to change lifestyle and reduce risk
- To maximise this opportunity to change behaviours, the following factors need to be addressed [ref]
  1. Information must be understood by the patient
  2. Information has to be meaningful to the patient
  3. Information has to be actionable
  4. Information must be reinforced

- **Provision of polygenic risk scores are most effective when managed through a suitably qualified medical practitioner rather than 'direct to consumer'.**