Scientist spotlight

# Transforming Alzheimer's disease characterization through genetic risk scoring

## Introduction

The health care paradigm is changing. Health care systems are moving from a model of sick care to preventive care. Predictive genomics is a dominant force driving the new paradigm. The Applied Biosystems™ Axiom™ Genotyping Solution delivers the population genotyping power that enables predictive genomics. With the Axiom Genotyping Solution, researchers can develop genomics tools that may ultimately diagnose disease earlier, predict outcomes more accurately, develop more personalized treatment strategies, and prescribe medications more safely.

Polygenic risk scoring (PRS) is a fundamental component of predictive genomics. PRS algorithms calculate the probability of a genetic disease trait emerging, health outcome prognosis, or an individual's likely response to medication. With a risk score, health care providers and patients have access to new genetic data that may contribute to personalized therapeutic strategies.

Nowhere is risk scoring more important than for early diagnosis, prognosis, and medication response for complex diseases that are currently unpredictable and untreatable such as cancer, heart disease, and Alzheimer's disease (AD).

Cytox is leading the way in AD risk scoring with genoSCORE-LAB, one of the first CE-marked PRS tests developed using the Thermo Fisher Axiom Genotyping Solution. We talked with Dr. Richard Pither, CEO of Cytox, to learn more about how the company is using polygenic risk scoring to change understanding of AD today and their vision for PRS in the future of health care.

**Richard Pither, PhD, CEO**

Cytox provides non-invasive, risk assessment and patient stratification tools for Alzheimer's disease (AD) and other forms of dementia. Cytox's vision is to transform how new treatments are developed, how people are screened and how patients with cognitive impairment are cared for. Cytox's genoSCORE™-LAB is a new microarray-based genotyping test that requires only a saliva sample to determine a polygenic risk score (PRS) to stratify risk in an individual with early AD indications.

**Thermo Fisher Scientific:** Why did you choose microarrays, and specifically the Axiom Genotyping Solution, as the platform for the genoSCORE-LAB test?

**Richard Pither (RP):** We need our test to be fast, reliable and cost-effective. Microarrays meet these criteria for us. We chose the Axiom Genotyping Solution because it has a long history of ease-of-use, robust data, and reliable performance.

Speed and cost are critical factors for drug developers to complete clinical trials quickly, make treatments available to patients as soon as possible and stay ahead of competitors. With genoSCORE-LAB, trial investigators can be confident in the variant calling results and move forward quickly. For health care providers, delivering news of AD risk can be a difficult conversation for the clinicians, patients, and families. Trust in the test results is vital to enable patients to take the most appropriate mitigating actions and manage the emotional and financial burdens of the disease.

As of 2020, 60% of people with dementia live in low- and middle-income countries [1]. It is important to us that our test is accessible for global use. The Axiom Genotyping Solution is easy to use and cost-effective, so it may be an excellent option for populations that have limited health care resources. In addition, patients with AD and other forms of dementia have cognitive impairments and many are elderly, which can make blood draws and other forms of testing challenging. We designed the genoSCORE-LAB test to require only a saliva sample to ensure it is easy to use for these individuals.

Our vision is to continually expand our testing capabilities. We needed a customized genotyping microarray that would evolve with us. We knew from the start that it would be critical to establish the right commercial and academic partnerships to support our vision.

**Richard Pither, PhD, CEO**

**Thermo Fisher Scientific:** What challenges did you face when you started this project?

**RP:** Our vision is to continually expand our testing capabilities. We needed a customized genotyping microarray that would evolve with us. We knew from the start that it would be critical to establish the right commercial and academic partnerships to support our vision. The deep technical expertise in genotyping and microarrays at Thermo Fisher Scientific has been key in designing and optimizing our custom variaTECT™ array. Together, we designed a panel of about 112,000 common variants linked to AD, along with age and gender covariants, which enabled us to build a robust PRS algorithm.

We are now expanding the ethnic and geographic diversity in our tests. As the diversity of available genotyping data grows, we will continue to refine and validate our array for a broader range of populations and eventually to other disease areas.

**Thermo Fisher Scientific:** How will Cytox's AD risk assessment tests impact health care?

**RP:** Age is the single biggest risk factor for developing AD, but genetics, lifestyle, comorbidities, and environment can also contribute. The opportunity to mitigate the impact of the disease through these other factors highlights the importance of early identification to enable early intervention.

Diagnosis of AD is challenging because the onset and progression of clinical manifestations such as memory loss, vision or spatial problems, or impaired judgement can be variable, gradual, or mistaken for other conditions. The single most influential genetic risk factor for late-onset AD is the E4 allele of apolipoprotein E (APOE e4) [2]. However, all individuals who carry the E4 allele may not develop AD and many individuals who do not carry the allele do develop AD. A genetic risk-scoring test such as genoSCORE-LAB will be extremely valuable to provide a more comprehensive view of an individual's genetic risk of AD.

99% of clinical trials for AD medications fail. Risk stratification with genoSCORE-LAB may help pharmaceutical companies to tailor, stratify, and select the most suitable cohorts; improve trial outcomes; and ultimately provide more effective AD treatments.

**Thermo Fisher Scientific:** What are the barriers to the integration of a PRS-based test into standard health care?

**RP:** Most importantly, any clinical test for genetic diseases must only deliver diagnoses for diseases that have known treatments with clear benefit to patient outcomes. Test results can only benefit the patient if the clinician can explain the testing and patients can understand and adhere to recommended therapies. This can be especially challenging for patients with impaired memory or judgement.

Insurance reimbursement is another barrier to adoption. It is encouraging to see some major insurers and health providers already proactively beginning to establish PRS reimbursement standards that may benefit millions of individuals, particularly in the US.

**Thermo Fisher Scientific:** How do you see PRS impacting preemptive healthcare in the future?

**RP:** PRS has the potential to transform disease diagnosis and treatment. Human medicine is improving and people are living longer. As of 2020, AD affects over 46 million people globally and this number is projected to reach 75 million in 2030 with an economic impact estimated to exceed $1 trillion per year [3]. We anticipate that PRS-based tools could reshape how new treatments are developed. PRS may also change how individuals are assessed for their risk of AD and how high-risk patients are managed. Individuals who are most at risk of cognitive decline due to AD could take earlier and more decisive action to manage their disease progression [1-5]. Ultimately, PRS holds the potential to reduce the growth rate of the human, economic, and healthcare costs of AD and other complex diseases.

## REFERENCES


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