



Advancing the screening paradigm for assessing Alzheimer's disease risk, from using genetic polygenic risk biomarkers for non-ApoE4 carriers to identifying subjects with amyloid plaques most likely to progress from Mild Cognitive Impairment to Alzheimer's disease

Dr Richard Pither, CEO, Cytox Ltd, July 2018

Introduction

Developing a treatment for Alzheimer's disease (AD) has proved to be expensive and high risk to date, with many high-profile failures along the way. New understanding of the mechanisms involved in developing Alzheimer's is highlighting the need for more inclusive, simpler, less invasive and more affordable diagnosis and screening tools to help identify disease risk, monitor disease progression and assess response to treatment. This is particularly essential in the selection and stratification of subjects for clinical trials and for large-scale cohort studies, where PET imaging is simply too expensive for large-scale efforts and genetic screening for ApoE4 carriers simply cannot predict risk for 60% of individuals that go on to develop the disease.

Advances in genetic analysis have enabled us to offer a new approach to developing DNA biomarkers for assessing the risk of an individual's chances of developing Alzheimer's disease. This provides a tool that is simpler and more cost-effective for recruiting subjects for participation in clinical trials and cohort studies.

TGEN + ADNI path. confirmed cases & controls

- 84% & 81% AUC in TGEN & ADNI respectively
- 10-16% improvement in AUC over ApoE alone

Performance in ApoE3 homozygotes

- 83% AUC in TGEN for ApoE3 homozygotes
- Able to stratify risk beyond ApoE4

ADNI AD conversions

- 70% AUC for predicting conversion from clinical MCI to AD in PET amyloid-positive subjects
- 112 convert from 262

In this white paper we will provide background on the challenging and changing landscape for assessing Alzheimer's disease risk, and how Cytox approaches provide paradigm changing alternatives. Specifically, using polygenic risk scoring approaches trained and tested for clinical phenotype using large and well characterized IGAP and GERAD data sets, combined with running performance testing on independently collected TGEN and ADNI data sets, Cytox has made the following advancements deemed to be significant when compared to traditional PET imaging and ApoE4 carrier screening approaches:

- 10-16% improvement in AUC over ApoE4 carrier screening alone has been demonstrated across two well characterised pathology confirmed cohorts (TGEN and ADNI), with meaningful effectiveness in identifying risk in ApoE4 negative individuals as well
- Importantly, an AUC of 83% for predicting pathology confirmed cases from controls was achieved when analysing ApoE3 homozygote subjects only. This set of individuals represent around 55% of the general population and can currently only be assessed as 'neutral' risk for development of Alzheimer's disease (ApoE4 carriers being considered higher risk and ApoE2 being considered of lower risk)
- 70% AUC for predicting conversion from mild cognitive impairment (MCI) to Alzheimer's disease in PET positive subjects, where in the study 112 of 262 subjects converted to Alzheimer's disease. Being able to easily and cost-effectively stratify between disease progressors and non-progressors clearly is of high importance to pharma and biotech developing therapies to slow or reverse the progression of Alzheimer's disease
- In addition, an AUC of 79% for predicting subjects with MCI.

Changing landscape

Dementia and specifically Alzheimer's disease, which accounts for approximately 60-80% of dementia cases, is a devastating, currently incurable, disease which has huge impact on the sufferers and their carer givers and is a massive burden for health and social care providers. The World Health Organization estimates that dementia currently affects around 50 million people worldwide with nearly 10 million new cases of dementia a year¹. This number is expected to rise to 82 million by 2030 and 152 million in 2050. The existing worldwide annual costs of dementia is US \$818 billion and is predicted to become a trillion dollars by 2018 – equivalent to the world's 18th largest economy.

The challenges in developing disease modifying therapies for Alzheimer's have been evidenced by the failure of several major clinical trials over the past few years. Developing a new drug is expensive and takes many years; the complexity of the disease and the size of clinical trials will have an impact on both. According to the UK Office of Health Economics², R&D costs are higher for neurology and Alzheimer's disease, than many other therapy areas, due to lower success rates and longer development times making trials expensive and high risk. Consequently, the success probabilities at different clinical phases for dementia drug development are consistently lower than those for all other therapy areas, with resulting caution in investment in such trials. In addition, trial designs have been inappropriate as Alzheimer's mechanisms have not been well characterised, leading to the enrolment of subjects not likely to benefit from the treatment during the trial period. There is strong evidence that the Alzheimer's disease pathogenic process, in the form of amyloid accumulation, appears to begin years before patients show any symptoms of memory loss, thereby offering an opportunity for therapeutic intervention. Treating patients who already have progressed to moderate disease to try to reduce amyloid plaque burden has not yet worked.

In reviewing lessons learned from the failed bapineuzumab and solanezumab trials, an EU/US/CTAD Task Force³ found a broad consensus that Alzheimer's disease should be treated during its earliest stages, together with a strong emphasis on biomarkers and a need for new biomarkers to help indicate which patients among those showing early signs of the prodrome of MCI will progress to Alzheimer's disease and how quickly.

Diagnostic tests

Whilst 50-60% of MCI patients are at high risk of progression to Alzheimer's, current prognostic methods for Alzheimer's disease are only 25-30% accurate in early MCI⁴. Strategies for clinical trials now include enrolling early stage prodromal and pre-symptomatic subjects, therefore a tool that can support the stratification of MCI patients to those at highest risk of developing Alzheimer's whilst reducing the number of expensive confirmatory imaging tests would benefit the patients, their carers, researchers and the whole healthcare system. The current gold standard which can help support definitive diagnosis includes a battery of cognitive testing (Petersen or Dubois Criteria), potentially combined with structural neuroimaging and/or PET amyloid imaging. While these tests are designed for Alzheimer's disease, they do not give a complete picture of the other underlying causes of the disease. Moreover, PET scans are expensive and not easily accessible, limiting their widespread and routine use. In addition to the value of early diagnosis in the context of today's patient management, having a cost-effective way of identifying patients that will benefit from new disease modifying therapies will be critical.

"For Alzheimer therapy to work effectively, we need to start to treat the disease very early. Genetic analysis is the most effective way of deciding who should be assessed for early disease. For this, we need to achieve an AUC of close to 80%, and this is just where the current array performs. It could be a real help in the trials arena and later in clinical practice."

Professor John Hardy, Chair of Molecular Biology of Neurological Disease, UCL Institute of Neurology, London

Biomarkers – opportunities

Biomarkers will be very useful at all stages of drug development as well as early diagnosis and this has been recognised in recently issued guidance from the FDA⁵ in which two stages of Alzheimer's disease development are defined:

- Stage 1: characteristic pathophysiologic changes of AD but no evidence of clinical impact (asymptomatic)
- Stage 2: characteristic pathophysiologic changes of AD and subtle detectable abnormalities on sensitive neuropsychological measures, but no functional impairment

Unfortunately, there are currently no validated risk biomarkers offering an accurate and practical approach to stratification of MCI subjects. To date blood and cerebrospinal fluid (CSF) biomarkers have proved unsatisfactory, due to safety, compliance and logistical issues and poor correlation with clinical diagnosis and progression.

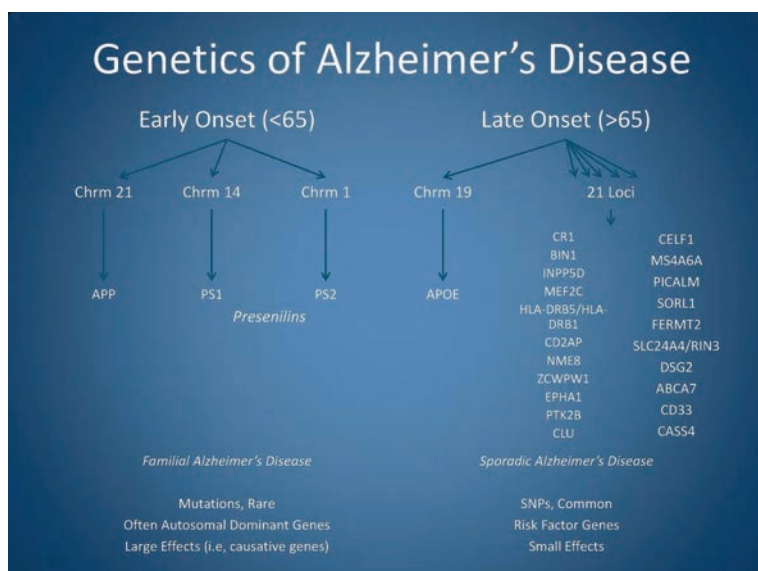
The ultimate goal in Alzheimer's disease, therefore, is an easy-to-use test, or combination of tests, that can stratify MCI patients and pre-symptomatic, at-risk subjects. Many pharma companies are focusing on treatments that delay the onset of Alzheimer's, making it increasingly important to identify this group.

Genetics of Alzheimer's disease

As well as having a clear heritable component, Alzheimer's disease is genetically complex. Neuropathologically, the disease is characterized by extracellular senile plaques containing β -amyloid (A β) and intracellular neurofibrillary tangles containing hyperphosphorylated tau protein. A relatively small number of dominant mutations in the amyloid precursor and presenilin genes are known to cause early onset Alzheimer's disease. Over the past two decades, genome-wide association studies (GWAS) have identified multiple loci and single nucleotide polymorphisms (SNPs) associated with the much more common, late-onset or sporadic form of the disease (LOAD)^{6,7,8,9}.

Apolipoprotein E (ApoE) is a major cholesterol carrier that supports lipid transport and injury repair in the brain. The ϵ 4 allele of ApoE (ApoE4) has been found to be a primary genetic risk factor for Alzheimer's disease^{8,9}, associated with increased risk for both early-onset Alzheimer's disease and LOAD^{6,7}. Although only 20-30% of humans are ApoE4 carriers, these individuals account for up to 40% of all Alzheimer's disease cases. In addition, ApoE4 is associated with an increased risk of lower age of onset^{10,11,12}, making this an important subset of the population at high risk of developing Alzheimer's disease. Tests are available for detecting ApoE gene variants, but these are not routinely used in clinical diagnosis as they do not provide a sufficiently informative marker when used alone. Nevertheless, an effective future biomarker panel will almost certainly include ApoE4 carrier status.

These genetic factors offer a ground-breaking new approach to developing a biomarker assay for assessing the risk of Alzheimer's disease.



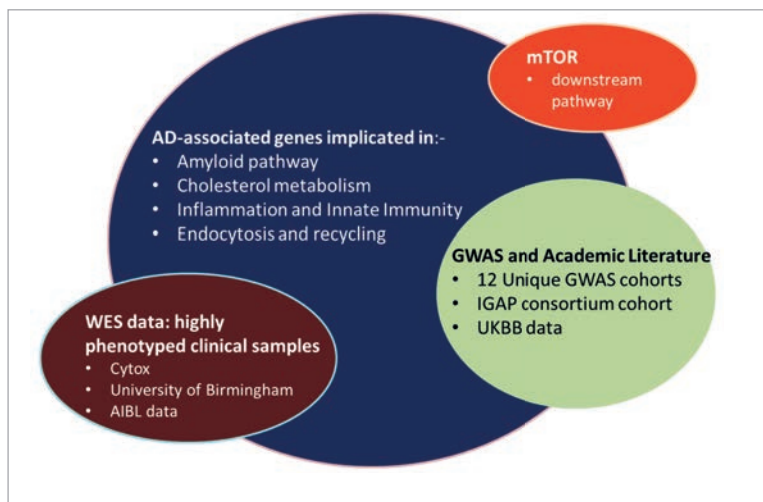
Genetics of Alzheimer's disease

An approach based on genetics and polygenic risk scoring

Cytox Limited is a precision medicine information company whose mission is to transform how treatments are developed, people are screened, and therapies are prescribed for the most prevalent neurological diseases, including Alzheimer's disease.

We are addressing this unmet need through the development of a polygenic risk score (PRS) approach based on our proprietary genetic SNP array, *variTECT*[™] and a range of predictive PRS algorithms. A polygenic risk score, also called a polygenic risk score, genetic risk score, hazard score or genome-wide score, is a number based on variation in multiple genetic loci and their associated weights together with age and gender co-variables, with the combined score offering a strong predictor of disease. The PRS approach, introduced originally by the International Schizophrenic Consortium¹³, serves as the best prediction for any trait that can be made when taking into account variation in multiple genetic variants. It has been reported that there is strong evidence for a large polygenic contribution to the overall heritable risk of late-onset Alzheimer's disease¹⁴(LOAD); and a further study has shown that polygenic score prediction captures nearly all common genetic risk factors for Alzheimer's¹⁵.

The *variTECT*[™] array content was developed through accessing publicly available genomic studies, coupled with multiple clinical research validation studies jointly run by Cytox and its global academic research collaborators, to identify the more than 100,000 SNPs which have been shown to be associated with biological pathways that are believed to be involved in Alzheimer's disease. *variTECT*[™] also contains SNPs associated with early-onset Alzheimer's, which is very rare, as well as other dementia types; these are useful for both QC purposes and allow future potential use for differential dementia diagnosis.



The Cytox *variTECT*[™] SNP array

This SNP array offers a simple research test requiring genomic DNA, which can be obtained from a blood or saliva sample, clinical sample archive or biobanked DNA. Genotyping on an array offers fast, robust, reproducible and cost effective results; *variTECT*[™] can be routinely analysed on the widely available Applied Biosystems[™] GeneTitan[™] Multi-Channel (MC) instrument platform from Thermo Fisher Scientific.

This is coupled with a proprietary software analysis package, SNPfitR[™], containing several different PRS algorithms which analyse the primary genotyping data from the array. The Cytox PRS algorithms have been validated against various end-points and can be used, amongst other things, to provide a risk score of the likelihood of the

presence of amyloid plaques – one of the hallmark pathologies associated with Alzheimer's disease. Whilst the presence of amyloid is not enough to confirm a diagnosis, those patients with MCI who have significant amyloid deposition are considered likely to be in the early pre-clinical stages of Alzheimer's disease. In addition to amyloid, other PRS algorithms evaluate a future risk of cognitive decline or provide specific insights into underlying signalling pathway deficits. Studies show PRS algorithms to be able to predict the presence of Alzheimer's disease related pathology in subjects who may have only mild symptoms or without symptoms at all. An AUC of up to 78.2% was found in a clinical Alzheimer's disease case-control study and up to 84% in pathologically confirmed case-control study¹⁶.

This range of analytical tools thus offers the possibility of customized and bespoke approaches to the analysis of genetic data, according to the specific interests and requirements of the study sponsor.

Ongoing development and validation of polygenic risk score algorithms

Cytox has worked with leading academic partners who have accessed and tested data from many large studies, including but not limited to the International Genomics of Alzheimer's Project (IGAP), Genetic and Environmental Risk in Alzheimer's Disease (GERAD), Translational Genomics Research Institute (TGEN) and the Alzheimer's Disease Neuroimaging Initiative (ADNI). By collecting data from well phenotyped individuals, both with and without amyloid plaques and with a range of clinical symptoms from cognitively normal through to Alzheimer's disease, Cytox and our collaborators have developed a number of mathematical algorithms which have been subsequently trialed and optimised using independent test sets to assess the performance of the assay^{17,18,19}.

"From a precision medicine standpoint, what is needed in Alzheimer's disease science is the identification of genetic signatures of specific subtypes of individuals most likely to benefit (or not benefit) from targeted therapies. The polygenic profiling approach has demonstrated utility for calculating an individual level genetic risk profile, that can predict disease development. Our analyses suggest that while as yet unknown, the majority of the remaining common variant susceptibility loci are captured, either directly or indirectly within the polygenic risk score model and is quite suitable for AD genetic risk prediction with accuracy between 74%-86%."

Professor Valentina Escott-Price and Professor Julie Williams, Director, Dementia Research Institute, School of Medicine, Cardiff University

Cytox is continuing to study well-phenotyped samples from a mix of both academic and pharma partners. These include: the Australian Imaging, Biomarker & Lifestyle Flagship Study of Ageing (AIBL), one of the largest, well-characterised, longitudinal cohorts of healthy ageing and cognitive decline in the world; the pioneering French INSIGHT study of Alzheimer's disease and one of the first in the world to monitor healthy subjects at risk; and a collaboration with eminent Alzheimer's disease researcher, Professor John Hardy at the UCL Institute of Neurology, London and Dr Zsuzsanna Nagy, Cytox's scientific founder – well known for her groundbreaking work on the involvement of the cell cycle in neurodegenerative diseases, at the University of Birmingham. This collaboration was awarded three-year funding from Innovate UK in 2015. In addition, Cytox is working with Mayo Clinic's Alzheimer's Disease Research Center, which will test current and new proprietary algorithms; and with the University of Cardiff, in which current algorithms will be tested in large cohorts of patients and cognitively normal subjects. The collaboration with the University of Cardiff has been awarded two-year funding from Innovate UK. The Cardiff team is renowned for its Alzheimer's research including pivotal research in dementia, Alzheimer's and neurodegenerative disease genetics, reporting a PRS with a PPV of 81% for predicting Alzheimer's disease risk¹⁴.

This approach provides a flexible integrated research platform that can encompass new content, such as familial markers for Alzheimer's risk and ApoE4 carrier status and evolve as the PRS algorithms are optimised.

Genetic risk score

Cytox is continuing to commercialise two analytical strategies using the Cytox *genoBAR*TM algorithm for genetically screening subjects for risk of developing Alzheimer's disease. Our hypothesis-based approach uses several hundred SNPs that we have identified through our collaborative research studies.

Cardiff algorithm performance in screening for future risk of Alzheimer's disease in pre-symptomatic subjects

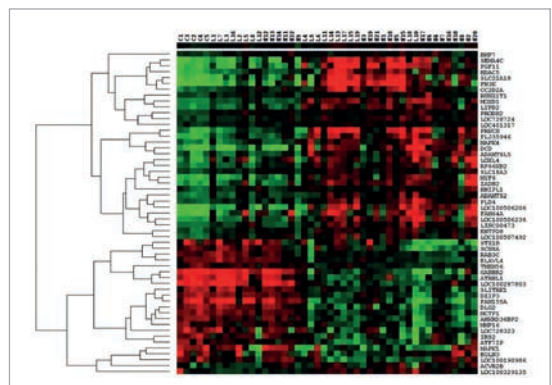
The Cardiff PRS approach uses logistic regression analysis utilising Alzheimer's disease associated SNPs reported by the IGAP consortium²⁰.

Evaluating the Cardiff model in various independent datasets, a recent study²¹ selected SNPs and identified risk alleles using GWAS data from 17,008 cases and 37,154 controls obtained from the IGAP. This dataset was imputed using the 1000 genomes data (release Dec 2010) as a reference panel. In 724 subjects from ADNI three assessments to predict clinical status were made and performance measured as AUC. The Cardiff PRS offered high accuracy in predicting clinical Alzheimer's disease (82%) and MCI (75%), and is ApoE4-independent so can be used to predict Alzheimer's in the whole population. The Cardiff PRS also offers great potential to stratify amyloid-positive subjects for risk of clinical progression from MCI to Alzheimer's disease and in doing so, providing significant benefit to pharma companies wishing to show benefits of their drugs on cognitive decline. Highlights include:

- 10-16% improvement in AUC over ApoE4 carrier screening alone has been demonstrated across two well characterised pathology confirmed cohorts (TGEN and ADNI), with meaningful effectiveness in identifying risk in ApoE4 negative individuals
- AUC of 83% for predicting pathology confirmed cases from controls was achieved when analysing ApoE3 homozygote subjects only
- 70% AUC for predicting conversion from MCI to Alzheimer's disease in PET positive subjects, where in the study 112 of 262 subjects converted to Alzheimer's disease
- AUC of 79% for predicting subjects with MCI.

genoTOR™ and its potential to target drugs in pathway-specific manner

Defects in cell cycle regulation play a fundamental role in several diseases. It is now widely accepted that the pathogenesis of Alzheimer's disease involves similar cell cycle mechanisms that could represent an important risk factor for the development of Alzheimer's disease and other dementias. Many cellular processes are regulated by the multitude of cellular signalling pathways downstream of- and influenced by the complex mTOR (mammalian target of rapamycin) pathway; differentially expressed mTOR pathway genes may regulate key functions linked to Alzheimer's disease^{22,23}. Research has identified genetic risk variants (SNPs) which can be used ultimately, in the definition of an algorithm to predict Alzheimer's disease progression. Proprietary data suggests that an assessment of disease risk may be possible using a customised genetic variation panel associated with mTOR signalling and other pathways. Molecular network approaches have been successful in several diseases. Cytox is actively developing new approaches designed to help its pharmaceutical customers better understand the role that the mTOR pathway plays in the development and progression of dementia. mTOR pathways regulate the adaptive response of cells to their environment and include the activation and inhibition of a large number of genes. The Cytox-Birmingham *genoTOR*™ algorithm calculates a SNP burden score for 21 different pathways associated with mTOR, providing insight into Alzheimer's disease subjects who phenotypically show similar symptoms, but genotypically may be quite different. *genoTOR*™-derived heat-maps can be used to further analyse the pathway-specific burdens in patients, thereby offering a more subtle stratification of trial subjects depending on the mechanisms of drug action.



genoTOR™-derived heat-map

The *genoTOR*™ PRS algorithm has been shown to be ApoE4-independent and can be used to stratify for clinical risk of Alzheimer's disease²⁰. The study further reported that *genoTOR*™ has potential to stratify within an Alzheimer's population and facilitate pathway-based population segmentation for targeted drug trials.

As pharmaceutical companies adjust their focus to develop more genetically targeted drugs to treat the progression of Alzheimer's disease, we believe that approaches like *genoTOR*™ will play an increasingly important and vital role.

Highly effective genetic risk stratification for Alzheimer's disease

This PRS approach has been developed and tested using multiple international cohorts on nearly 2,500 pathology confirmed subjects, with the presence of amyloid being quantitatively determined by PET, CSF or post-mortem autopsy. Results have been as high as 95% PPV for the presence of amyloid in some cohorts and some also show greater than 10% AUC improvement over tests that measure ApoE4 carrier status alone. ApoE4 carrier screening is effective only in ApoE4 carriers only – approximately 25% of the population. The Cytox PRS approach is ApoE4 independent and so can be used to stratify for Alzheimer's and MCI in ApoE4 non-carriers.

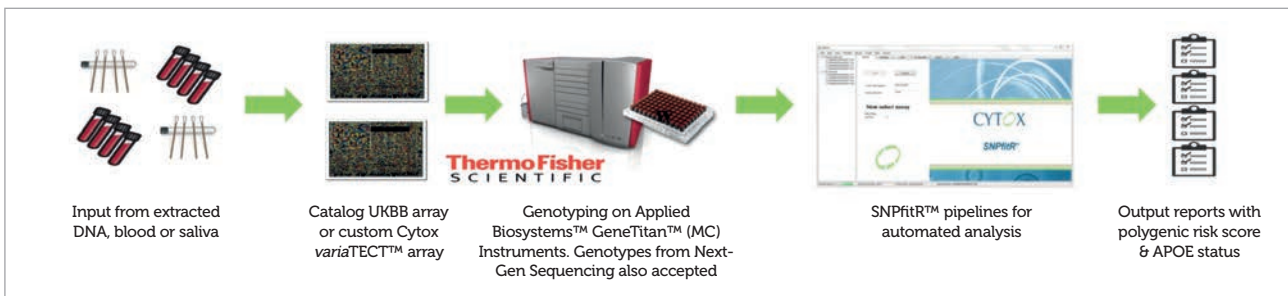
We have undertaken modelling studies to assess the potential in cost and time savings of applying this approach to stratify individuals for future risk of developing Alzheimer's disease in clinical trial screening for patient recruitment. Assuming a population with 30% amyloid positive rate and PET amyloid imaging procedure costs ranging from \$5,000 - 10,000, a Cytox test performance of 80% sensitivity and 80% specificity would offer an approximate saving of \$15,000/trial subject recruited.

It can be seen, therefore, that applying this simple test at the earliest stage of the recruitment screening process can offer effective triage of prospective clinical trial subjects, with the potential to stratify risk of cognitive decline within an amyloid-positive pre-symptomatic or MCI population. This both reduces the numbers of amyloid positive subjects lost before enrolment and reduces the number of PET scans needed to identify amyloid positive subjects. An ideal approach that meets the market requirement for large-scale precision medicine screening for Alzheimer's risk.

Cytox's approaches are being actively evaluated today by pharma partners as a more rigorous, simple and cost-effective means to improve stratification of at-risk subjects for participation in clinical trials.

Strategic global partners

The *variTECT*[™] panel utilises the proven power and scalability of the Applied Biosystems[™] GeneTitan[™] Multi-Channel (MC) Instrument platform from Thermo Fisher Scientific. This ensures an easy, straightforward process, which is provided as a service through our strategic partners.



Cytox has partnered with leading CLIA-compliant genomic laboratories in both North America (AKESOGen) and Europe (Eurofins Genomics) to offer Alzheimer's disease risk assessment globally to pharma, biotech and research labs pursuing clinical research and drug development in Alzheimer's disease and our assays can be performed by service laboratories equipped to run the Applied Biosystems[™] GeneTitan[™] Multi-Channel (MC) Instrument platform anywhere in the world.

AKESOGen is a highly experienced biomarker, genomics and pharmacogenomics contract research organization performing biomarker profiling and genomics services utilizing different types of markers for clients in biotech, pharmaceutical, academic and government research/testing. Based in Atlanta, Georgia, the company offers CLIA compliant lab with strict process controls.

Eurofins Genomics, a member of the Eurofins Group with facilities in Europe, is an internationally leading provider of DNA sequencing services, genotyping services, DNA synthesis products and bioinformatics services for pharma, diagnostics, food, agriculture, biotechnological and research markets.

In addition to our goal of making the Cytox assay set available worldwide, core to our business model is in-licensing, validating and deploying genetic content developed by the broader research community.

Summary

A novel genetic polygenic risk score approach to assessing the risk of developing Alzheimer's disease offers the potential of a new tool to help researchers and clinicians access the biology and genetics behind dementia, stratify patients to enable more cost effective and information rich clinical trials, and ultimately establish risk for cognitive decline and matching with the most appropriate targeted therapy. The Cytox integrated platform, available on a global basis for clinical sample testing, offers the possibility of customized and bespoke approaches to the analysis of genetic data, as well the ability to efficiently in-license and commercially deploy other investigator options.

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