Stratification of individuals for PET amyloid positivity and Alzheimer's Disease risk using polygenic risk score analysis – new opportunities for clinical trial design

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Background

- Heterogeneity of patient populations and lack of early diagnostic markers have been cited as factors in the last 15 years of clinical trial failures in Alzheimer's disease (AD) therapeutics.
- PET amyloid imaging and/or CSF amyloid testing are established techniques in selection of subjects for clinical trials irrespective of the therapy target. The challenge to identify pre-symptomatic individuals who are likely to suffer future cognitive decline remains.
- Using polygenic risk score (PRS) algorithms, it is possible to improve stratification prior to expensive and/or invasive confirmatory tests; particularly important in trials recruiting pre-symptomatic subjects where prevalence of amyloid positivity is low and risk of disease progression highly variable.
- PRS algorithms that examine the genetics associated with underlying mechanistic pathways thought to be involved in the development and progression of AD, may also offer opportunities to better understand drug response.
- A panel of 130,000 SNP DNA variants has been prepared (variaTECT™) in partnership with ThermoFisher Scientific, comprising a comprehensive list of variants associated with pathways relating to AD.
- All samples are genotyped on variaTECT™ (Axiom™) plates and processed on a GeneTitan® scanner. The SNPfltR™ analysis package provides an automated platform using raw genotyping data to produce multiple PRS based risk assessments.
- The Cardiff PRS approach uses logistic regression analysis utilising AD associated SNPs reported by the IGAP consortium.
- The Birmingham genoTOR™ algorithm is based on theoretical knowledge of the pathways involved.
- The Cardiff and Birmingham models have been evaluated in various independent datasets.

The Cytox Analysis

- SNPfitR™ takes processed files from Axiom™ Analysis Suite, utilising the genotyped SNP calls to produce risk estimates based on multiple available PRS algorithms.
- Detailed performance parameters are available within the software to facilitate detailed data interrogation.
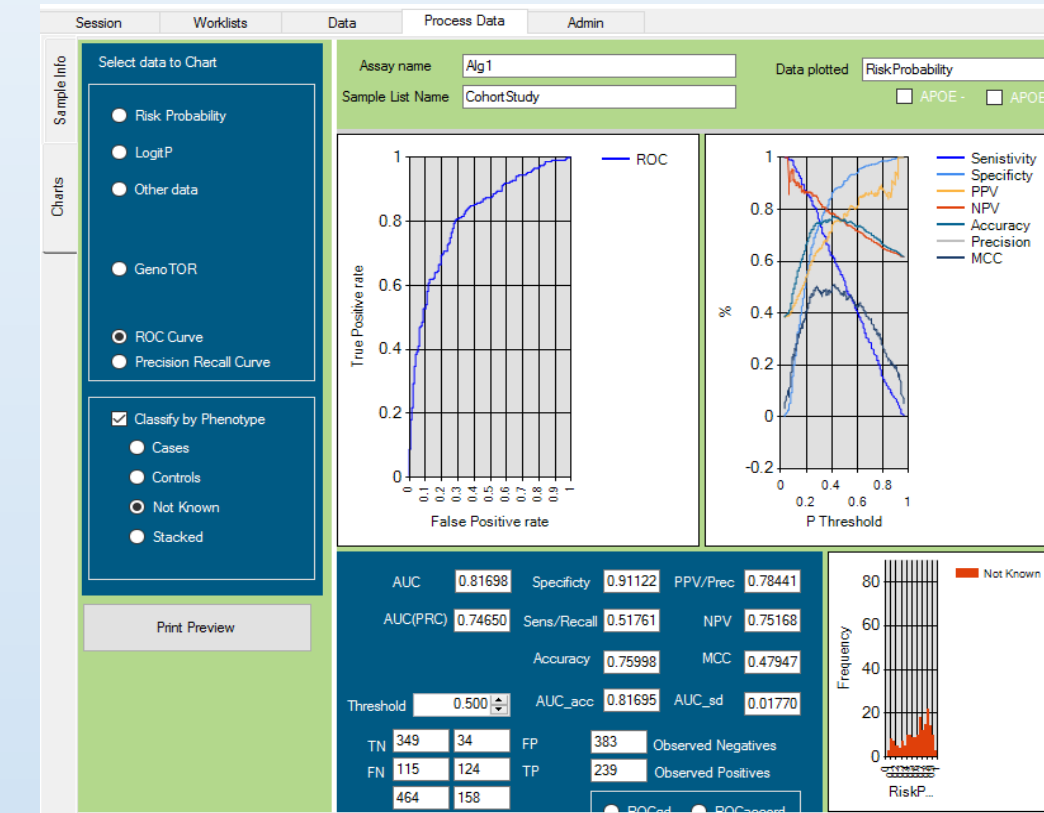
Cytox variaTECT™ SNP Array delivers the most comprehensive panel available today for the interrogation of over 130,000 Alzheimer's Disease informative SNPs
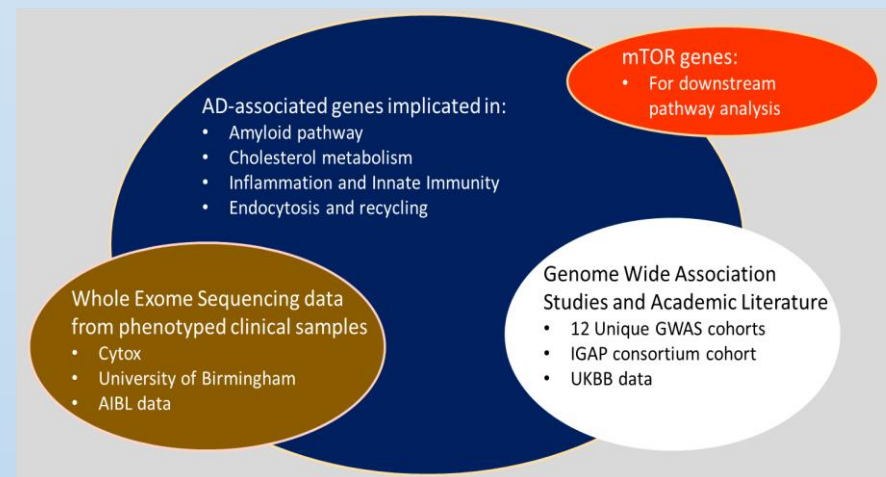

- Genotyping data from both the variaTECT™ array and the UKBiobank array can be used to generate the data required to drive the algorithms within SNPfitR™
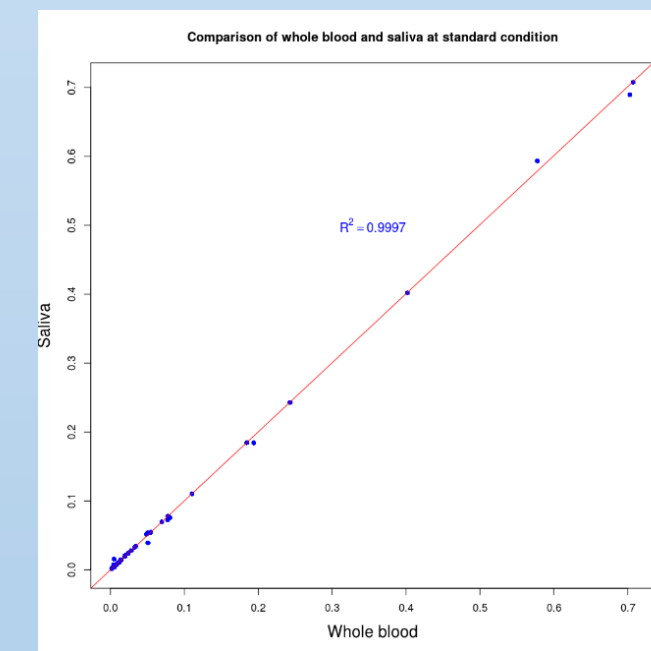
- Matched blood and saliva samples from 49 donors generate near identical genotyping on the variaTECT™ array and therefore near identical risk prediction in SNPfitR™
- Use of non-invasive sampling procedures facilitates easier and larger sample set collection.
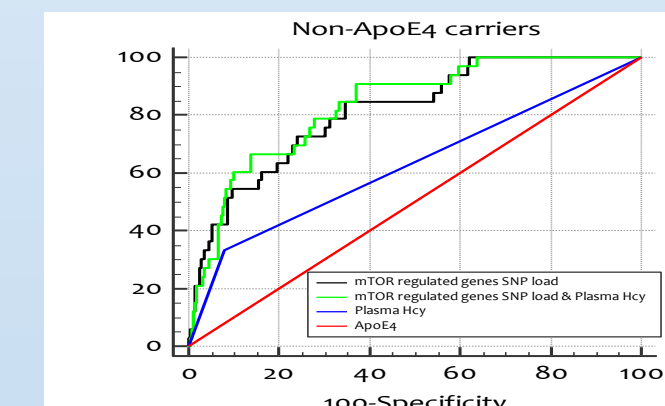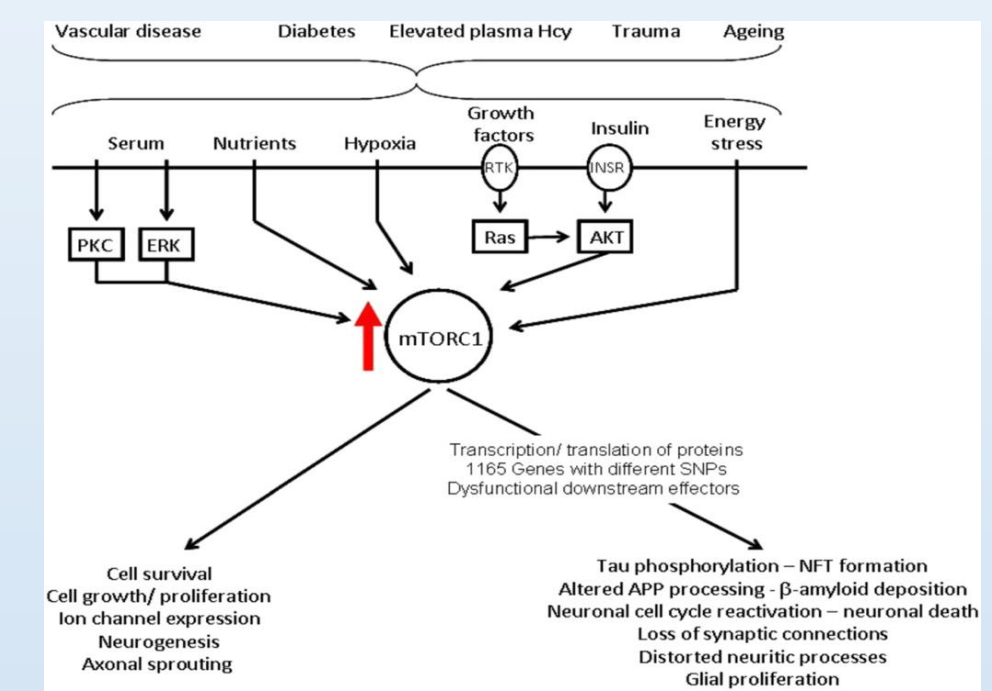

The Cardiff Algorithm

- Polygenic risk score (PRS) analysis tests whether the risk alleles identified in one association study were significantly enriched in the cases relative to the controls in an independent study. The first dataset is used to select the SNPs, the risk score alleles and their genetic effects. The second dataset is used to test whether the polygenic risk scores differ in cases and controls.
- Measures of polygenic burden could prove useful in distinguishing patients with Alzheimer's disease whose disease liability is most likely to carry a large or small genetic component. It has been shown that PRS has utility for calculating an individual level genetic risk profile that can predict disease development (AUC is up to 78.2% in a clinical AD case/control study and up to 84% in pathologically confirmed case/control study [2]).
- To select SNPs and identify risk alleles we used genome wide association data from 17,008 cases and 37,154 controls obtained from the International Genomics of Alzheimer's Project (IGAP) [3]. This dataset was imputed using the 1000 genomes data (release Dec2010) as a reference panel.
- In 724 subjects from ADNI [4] three assessments to predict clinical status were made 1) predicting AD cases vs cognitively normal controls (CNC), 2) predicting MCI cases vs CNC, 3) predicting progression of amyloid positive MCI cases that have subsequently converted to a clinical diagnosis of AD. The performance was measured as AUC.
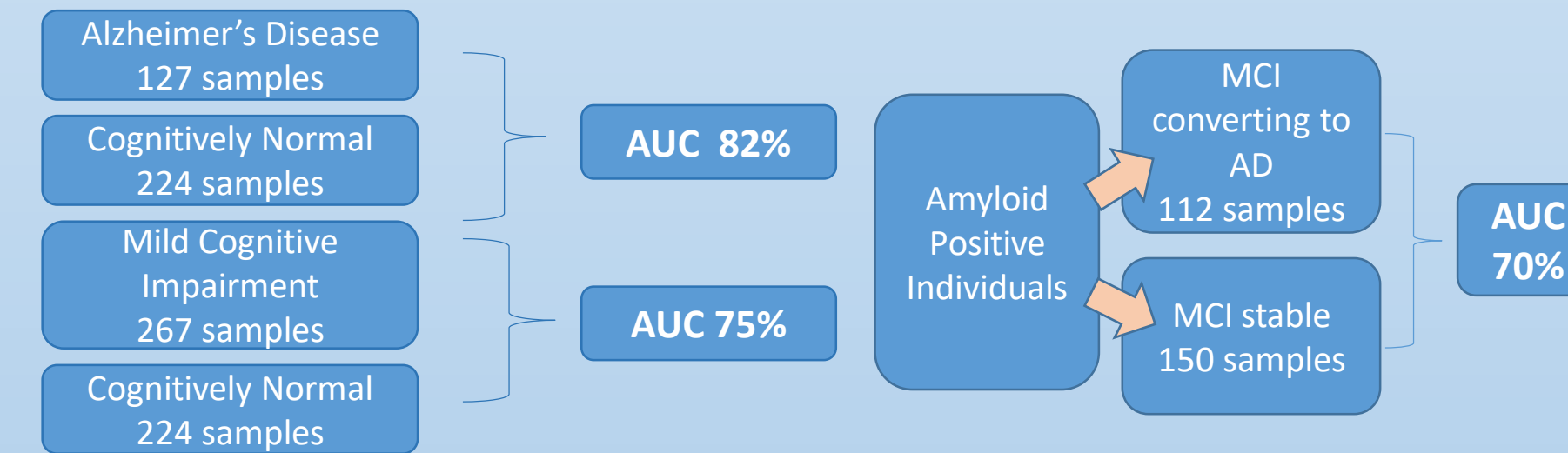
[1] Escott-Price et al (2015) Brain, doi: 10.1093/brain/awv268
[2] Escott-Price et al (2017) Annals of Neurology 82(2):311-314
[3] Lambert et al (2014) Nature Genetics 45(12):1452-8.
[4] http://adni.loni.usc.edu/
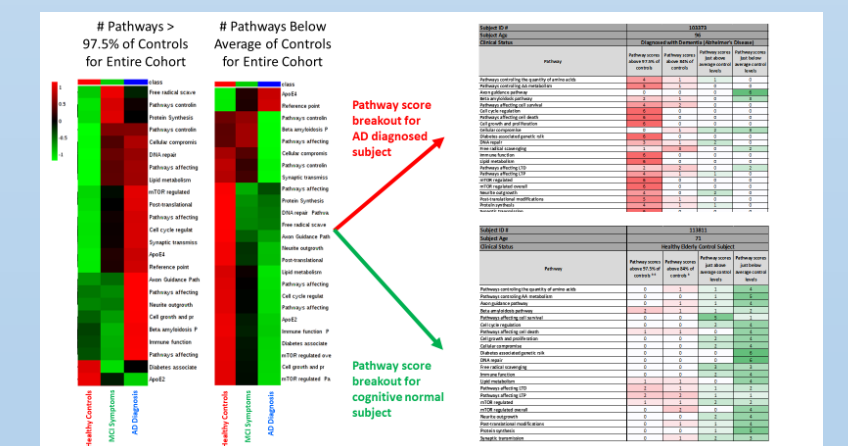
The Birmingham genoTOR™ Algorithm

- The molecular pathways disrupted in AD are well documented by several different approaches and many studies.
- The genes have known molecular functions and interactions with well documented SNPs (including their functional consequences).
- Molecular network approaches have been successful in several diseases.

- Comparison ROC analysis indicates that the genoTOR™ risk score is independent of the ApoE genotype and contributes significantly to AD risk identification.

- genoTOR™ generates pathway score profiles at an individual sample level facilitating patient selection and stratification.
- Cohort-specific differences can inform novel therapeutic targets.
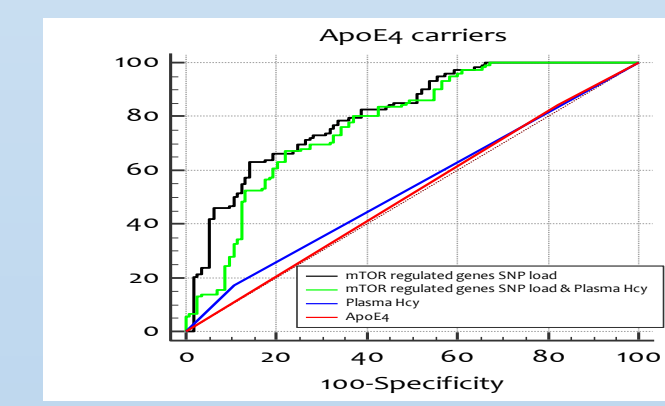
The Cytox Platform

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

Catalogue UKBB array or custom Cytox variaTECT™ array

Genotyping on Applied Biosystems GeneTitan™ MC Instruments. Genotypes from Next-Gen Sequencing also accepted

SNPfitR™ pipelines for automated analysis

Output reports with polygenic risk score & ApoE status
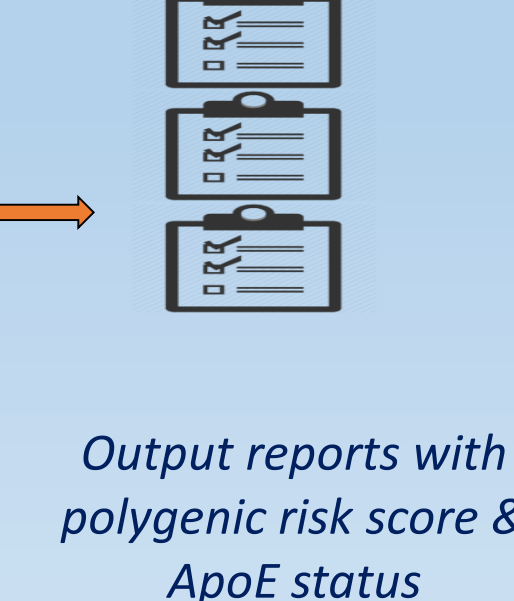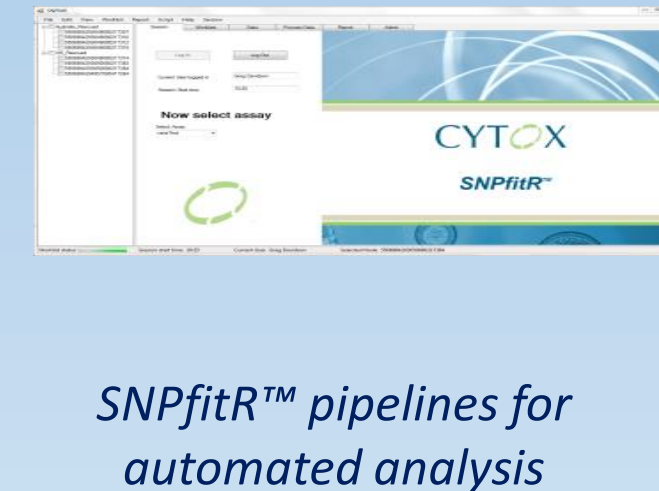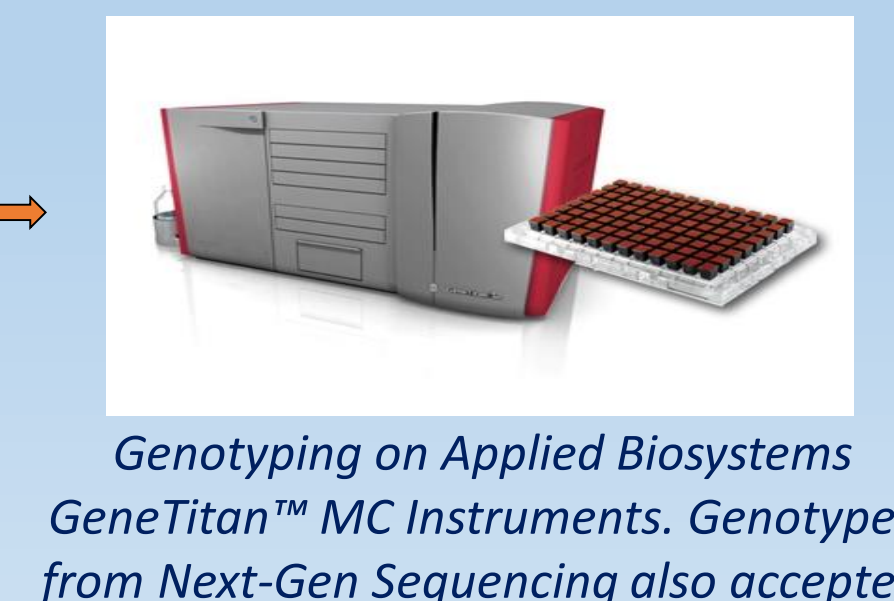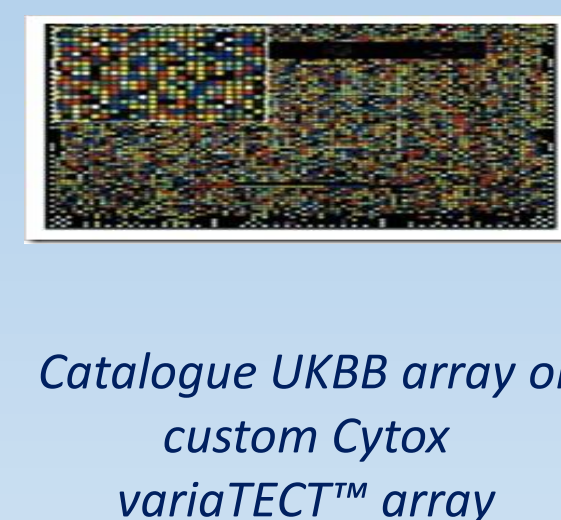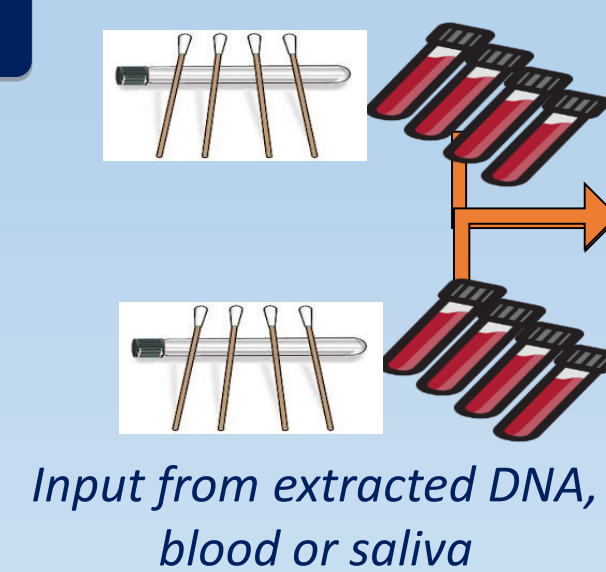
Conclusions

- Cardiff PRS offers high accuracy in predicting clinical AD and MCI and is ApoE-independent so can be used to predict Alzheimer's in whole population.
- Cardiff PRS can be used to stratify amyloid-positive subjects for risk of clinical progression from MCI to AD.
- The Birmingham genoTOR™ PRS algorithm is ApoE4-independent and can be used to stratify for clinical risk of AD, has potential to stratify within an AD population and facilitate pathway-based population segmentation for targeted drug trials.
- Integrated Cytox platform available on a global basis for clinical sample testing.