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STRATIFICATION OF PRE-SYMPTOMATIC AND COGNITIVELY NORMAL INDIVIDUALS USING POLYGENIC SCORING

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Disclosures

Dr Richard Pither: Full-time employee of Cytox Ltd

Dr Maryam Shoai: UCL; Funded under a Cytox-led, Innovate-UK project

Professor John Hardy: UCL; Co-recipient of a Cytox-led, Innovate-UK project

Professor Valentina Escott-Price: University of Cardiff; Former consultant for Cytox on Innovate-UK project

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Biomarkers are Crucial for the Early and Cost Effective Identification of AD Risk

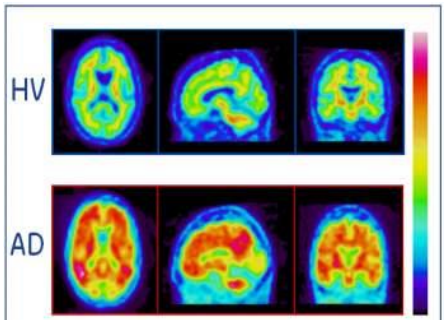
"Genetic analysis is the most cost effective and reliable way of deciding who should be assessed for early disease."

– Professor John Hardy –

Head of the Department of Molecular Neuroscience and Chair of Molecular Biology
of Neurological Disease at the UCL Institute of Neurology, London, England

Fellow of the Royal Society since 2009

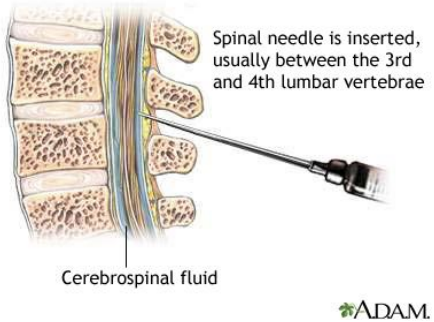
THE PROBLEM: Current methods for early assessment are expensive; have limited availability; are invasive and high risk; and show limited reproducibility



Brain Amyloid Imaging

PET – Positron Emission Tomography

PET Imaging is expensive and has limited availability - it is not a solution for larger scale studies or broader population screening



Lumbar Puncture

CSF – amyloid and tau fragments

Lumbar Puncture followed by protein analysis is highly invasive and high risk – it also has limited reproducibility at earlier stages of Alzheimer's disease

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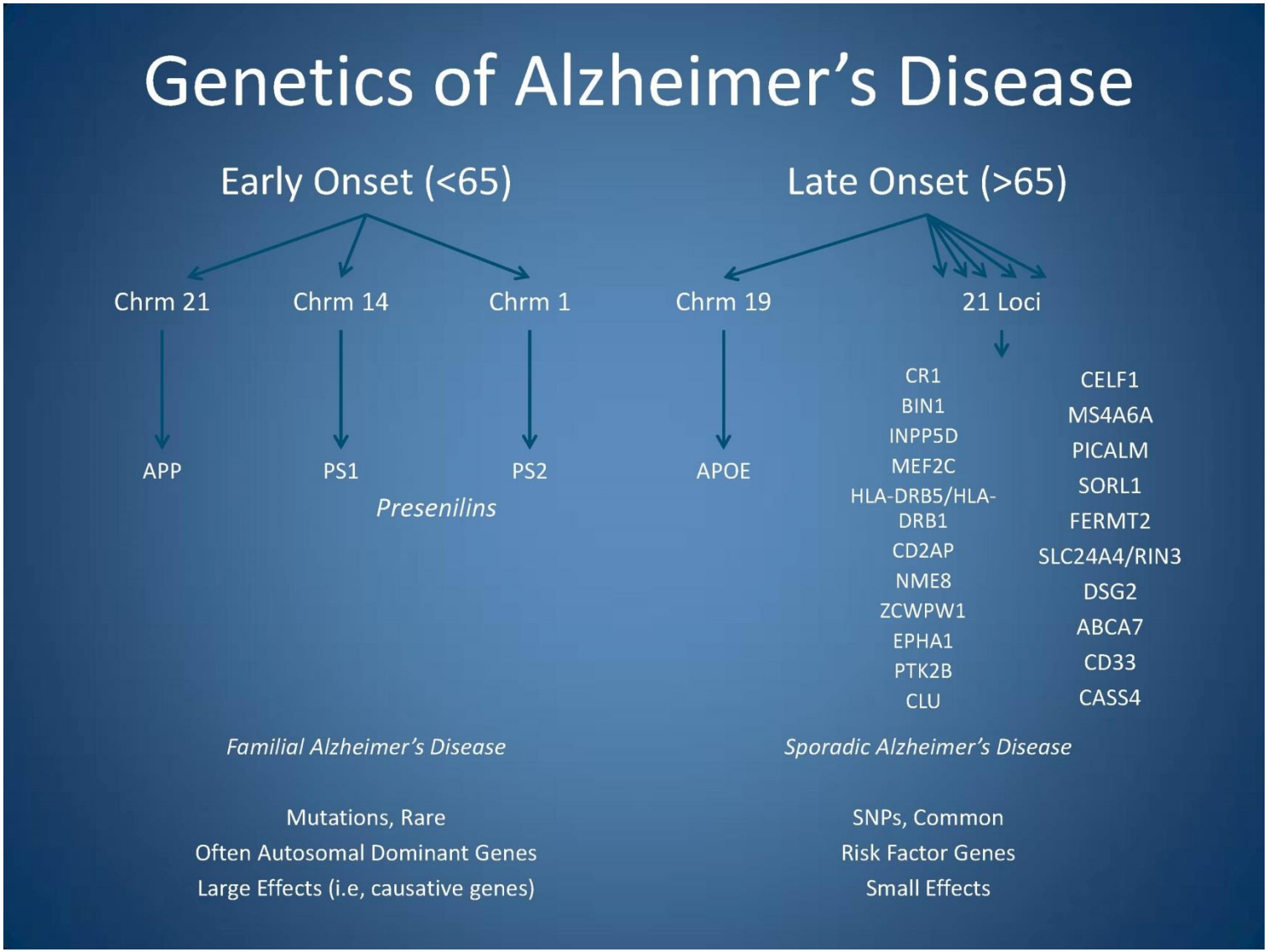
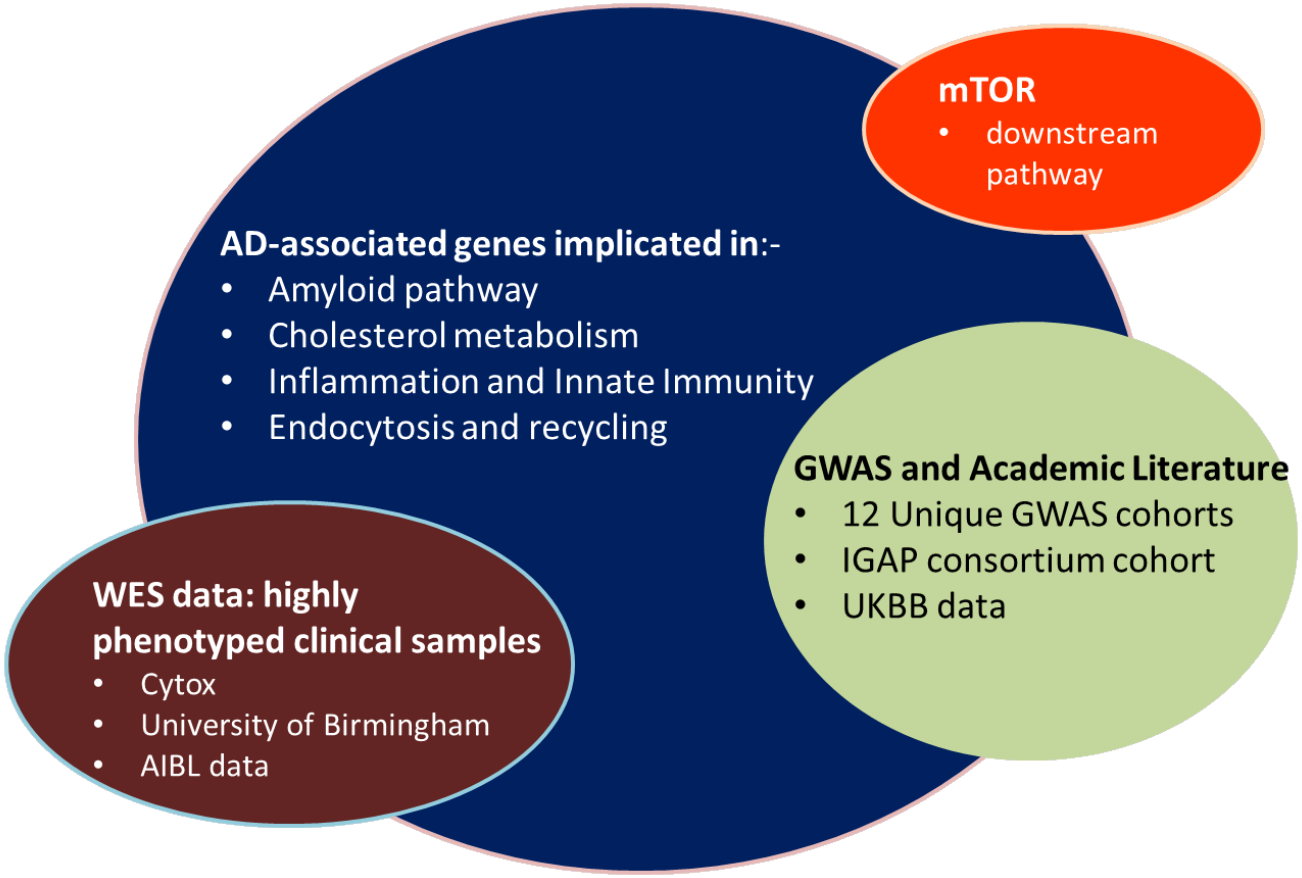
The Genetics of Alzheimer's Disease



The Cytox *varia*TECT™ array: ~130k SNPs

Cytox *varia*TECT™ SNP Array: comprehensive panel available today for the interrogation of over 130,000 Alzheimer's Disease informative SNPs



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Polygenic Risk Score: Training and Validation

- **Two basic approaches for variable selection and algorithm training**
  - Alg 1 (model 1): Hypothesis-based SNP selection
  - Alg 2 (model 2): Hypothesis-free variant selection using Elastic Net Regularisation

- **Polygenic Risk Scoring models trained and tested on PET amyloid or CSF confirmed specimens**
  - All confirmed cases with an appropriate number of controls
  - All cases and controls meet stringent clinical criteria with biomarker confirmation (amyloid PET and/or CSF)

- **Blinded validation in clinically assessed, post-mortem, pathology-confirmed cases and controls**
  - Validation samples obtained from;
    - UPenn (Brain Bank): John Trojanowski, Virginia Lee, Vivianna Van Deerlin, David Irwin (237 specimens)
  - True Positive Rate of 95% or greater
  - True Negative Rate around 76% is possible

- **Models yield results significantly better than what is currently available today**
  - For both ApoE4 negative cohorts and ApoE4 mixed cohorts

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Sample Cohort Characteristics (for information)

	Mean Age for: (years)							Proportion of : (%)						
Dataset	**dataset**	**Aβ +ve**	**Aβ -ve**	**E4+ve**	**E4-ve**	**Females**	**Males**	**females**	**males**	**Aβ +ve**	**Aβ -ve**	**E4+ves**	**E4+ve & Aβ -ve**	**E4+ve & Aβ +ve**
ADNI (678)	**76.43**	76.74	76.06	75.05	77.50	75.53	77.16	**44.99**	55.01	**53.98**	46.02	43.81	10.62	**33.19**
UPENN (252)	**81.56**	82.64	76.76	81.94	81.19	82.82	80.20	**51.59**	48.41	**82.14**	9.92	49.21	1.19	**46.03**
Cytox (119)	72.93	74.54	71.24	74.17	71.72	73.40	72.53	46.22	53.78	51.26	48.74	49.58	12.61	36.97
Leuven (162)	68.99	70.08	68.80	68.35	69.65	68.13	69.69	44.44	55.56	14.81	85.19	50.62	40.74	9.88
AIBL (613)	71.18	73.81	69.53	71.88	70.80	70.60	71.84	53.67	46.33	38.50	61.50	34.91	11.26	23.65
TGEN (1572)	81.64	82.06	80.91	81.13	82.13	83.19	79.43	58.84	41.16	63.74	36.26	48.54	7.32	41.22
INSIGHT (271)	76.05	76.79	75.87	76.55	75.93	76.09	75.98	64.21	35.79	19.56	80.44	18.82	10.70	8.12

…with thanks to our scientific collaborators

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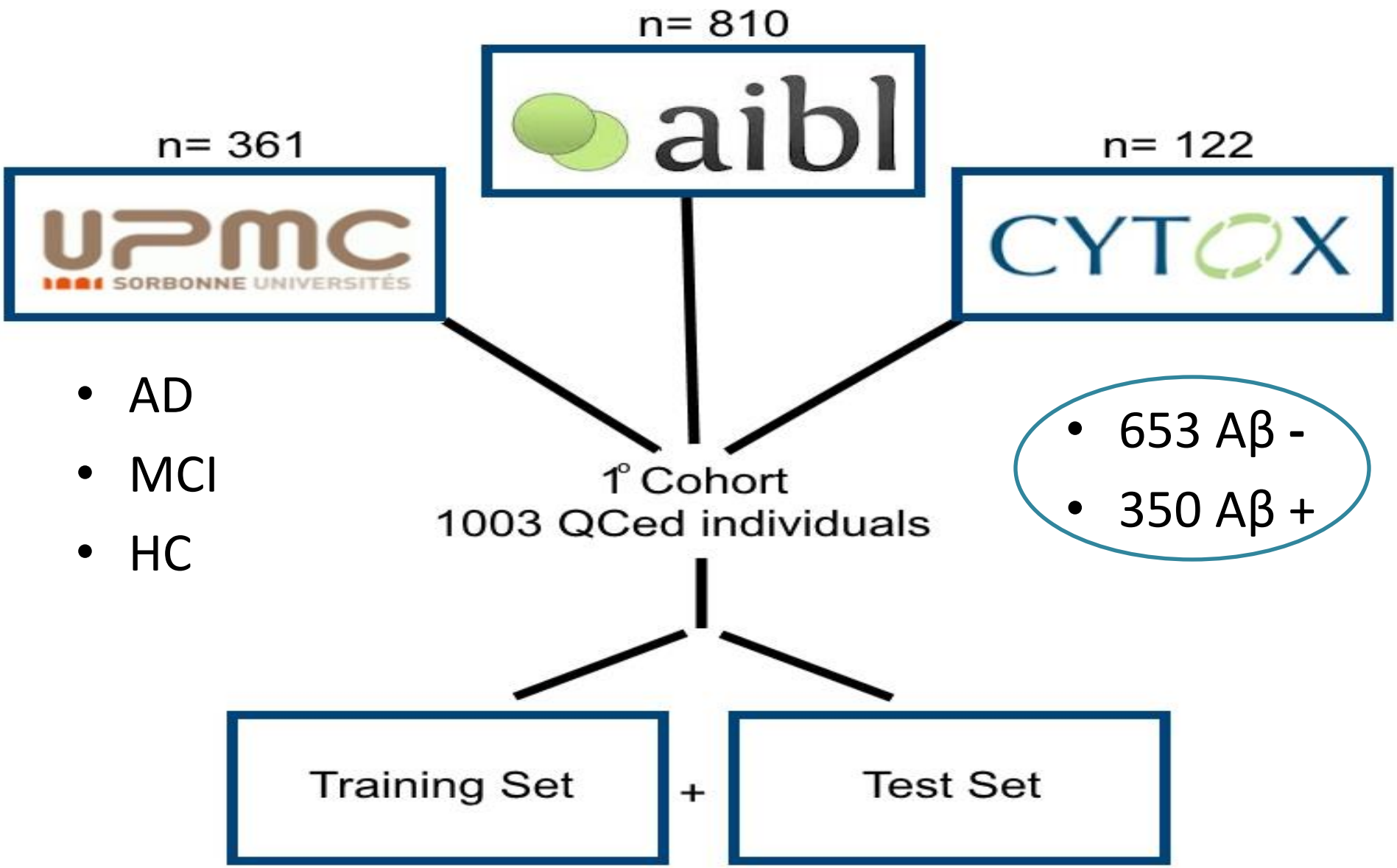
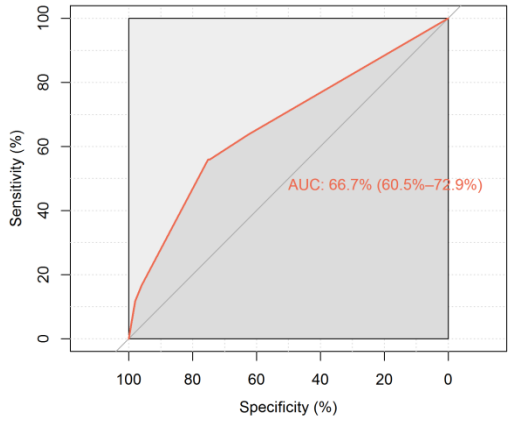
Training Cohort



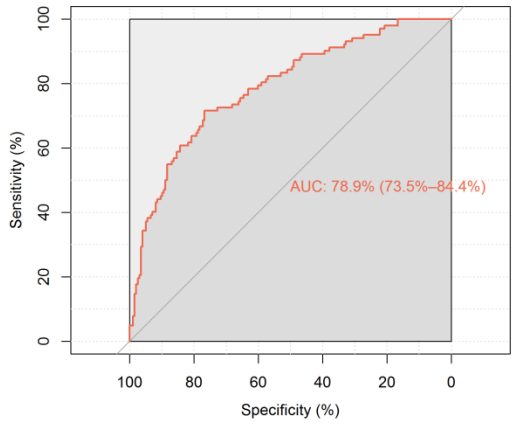
Model 1: performance on amyloid-positive subjects, with or without cognitive impairment

Stratification of Amyloid +ve subjects with or without cognitive impairment - *Significant improvement over current ApoE*

APOE baseline



APOE + Model
+ age and gender



name	Sensitivity	Specificity	AUC	L95	U95	PPV_33	NPV_33
Model1	54.902	55.051	59.546	52.556	66.003	70.071	39.430
APOE baseline	63.730	66.716	66.716	60.535	72.897	74.602	50.055
Model1 + APOEgenotyped	72.549	72.222	76.198	70.265	82.132	79.929	63.310
Model1 +APOEgenotyped+age+sex	72.549	72.727	78.931	73.503	84.360	80.116	63.625

Model could be used irrespective of APOE status

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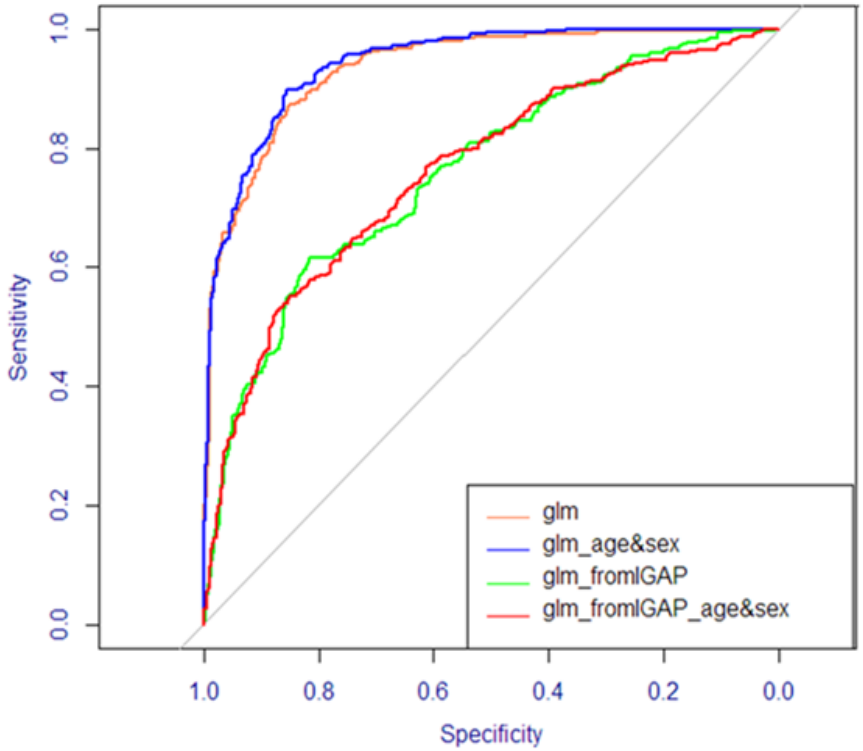
Model 2: Unbiased variable selection

- Train on the QC'ed samples
- Elastic net regression
- 10 fold cross validation
- Tested for selection stability
- Alpha = 0.5



name	Effect	NSNPs	Sensitivity	Specificity	AUC	L95	U95	PPV	NPV
glmmodel	2.829	159	85.71%	85.76%	**93.56%**	92.06%	95.06%	88.73%	82.10%
glmmodel_age&sex	2.986	159	86.29%	86.22%	**94.35%**	93.02%	95.68%	89.07%	82.85%

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Validation on post-mortem pathology-confirmed tissue: post un-blinding

- AD cases: Primary diagnosis of AD, secondary pathology cannot be ALS, FTLD-TDP, DLB, PD ; No familial cases with APP or PSN mutations
- Controls: Unremarkable Adult brain with Braak and CERAD less than 1

name	Effect	p	R2	Sensitivity	Specificity	AUC	L95	U95	PPV	NPV
APOE	1.715	2.06E-04	0.221	75.85%	76.00%	81.00%	72.81%	89.20%	86.46%	60.88%
age and gender	0.136	1.03E-04	0.144	68.60%	68.00%	72.85%	58.34%	87.36%	81.47%	51.36%
Model1	0.681	1.67E-03	0.089	63.29%	64.00%	70.59%	61.28%	79.90%	77.97%	46.40%
Model1 + APOE	2.247	2.94E-05	0.304	79.71%	80.00%	85.64%	78.13%	93.16%	88.90%	66.25%
Model2 + APOE	1.210	1.91E-04	0.163	70.05%	72.00%	75.27%	66.89%	83.64%	82.99%	55.20%

- Blind validation of models:
  - True Positive Rate around 90% or greater
- Models sensitive to proportion of MCIs
- Improvement on going using more samples and alternative machine learning techniques

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Polygenic risk score algorithms for AD – an active field…..

doi:10.1093/brain/awv268 BRAIN 2015: 138; 3673–3684 | 3673

BRAIN
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Common polygenic variation enhances risk prediction for Alzheimer's disease

Valentina Escott-Price,[1] Rebecca Sims,[1] Christian Bannister,[1] Denise Harold,[2] Maria Vronskaya,[1] Elisa Majounie,[1] Nandini Badarinarayan,[1] GERAD/PERADES,* IGAP consortia,* Kevin Morgan,[3] Peter Passmore,[4] Clive Holmes,[5] John Powell,[6] Carol Brayne,[7] Michael Gill,[8] Simon Mead,[9] Alison Goate,[10] Carlos Cruchaga,[11] Jean-Charles Lambert,[12,13,14] Cornelia van Duijn,[15] Wolfgang Maier,[16,17] Alfredo Ramirez,[16,18] Peter Holmans,[1] Lesley Jones,[1] John Hardy,[19] Sudha Seshadri,[20] Gerard D. Schellenberg,[21] Philippe Amouyel[12,13,14,22] and Julie Williams[1]

*Data used in the preparation of this article were obtained from the Genetic and Environmental Risk for Alzheimer's disease (GERAD) (which now incorporates the Defining Genetic, Polygenic and Environmental Risk for Alzheimer's Disease using multiple powerful cohorts, focused Epigenetics and Stem cell metabolomics, PERADES consortium) and the International Genomics of Alzheimer's Disease (IGAP) Consortia. For details of these consortia, see Appendix I and the Supplementary material.

Annals of NEUROLOGY
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BRIEF COMMUNICATION

Polygenic Hazard Scores in Preclinical Alzheimer Disease

Chin Hong Tan, PhD,[1] Bradley T. Hyman, MD, PhD,[2] Jacinth J. X. Tan, PhD,[3] Christopher P. Hess, MD, PhD,[1] William P. Dillon, MD,[1] Gerard D. Schellenberg, PhD,[4] Lilah M. Besser, PhD,[5] Walter A. Kukull, PhD,[5] Karolina Kauppi, PhD,[6] Linda K. McEvoy, PhD,[6] Ole A. Andreassen, MD, PhD,[7] Anders M. Dale, PhD,[6,8,9] Chun Chieh Fan, MD,[9]* and Rahul S. Desikan, MD, PhD[1,10]*

Identifying asymptomatic older individuals at elevated risk for developing Alzheimer disease (AD) is of clinical importance. Among 1,081 asymptomatic older adults, a recently validated polygenic hazard score (PHS) sig-

Beyond *APOE* ε4 carrier status, recent genetic studies have identified numerous single nucleotide polymorphisms (SNPs), each of which is associated with a small increase in AD dementia risk.[6] Using genome-wide association studies (GWAS) from AD cases and controls, we have recently developed a novel polygenic hazard score (PHS) for predicting age-specific risk for AD dementia that integrates 31 AD-associated SNPs (in addition to *APOE*) with U.S. population-based AD dementia incidence rates.[7] Among asymptomatic older adults, in retrospective analyses, we have previously shown that the PHS-predicted age of AD onset strongly correlates with the actual age of onset.[7] To evaluate clinical usefulness and further validate PHS, in this study, we prospectively evaluated whether PHS predicts rate of progression to AD dementia and longitudinal cognitive decline in cognitively asymptomatic older adults and individuals with MCI.

Subjects and Methods

We evaluated longitudinal clinical and neuropsychological data (from March 2016) from the National Alzheimer's Coordinating Center (NACC).[8] Using the NACC uniform dataset, we focused on older individuals classified at baseline as cognitively

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Cascaded Multi-view Canonical Correlation (CaMCCo) for Early Diagnosis of Alzheimer's Disease via Fusion of Clinical, Imaging and Omic Features

Asha Singanamalli[1], Haibo Wang[1], Anant Madabhushi[1] & Alzheimer's Disease Neuroimaging Initiative*

The introduction of mild cognitive impairment (MCI) as a diagnostic category adds to the challenges of diagnosing Alzheimer's Disease (AD). No single marker has been proven to accurately categorize patients into their respective diagnostic groups. Thus, previous studies have attempted to develop fused predictors of AD and MCI. These studies have two main limitations. Most do not simultaneously consider all diagnostic categories and provide suboptimal fused representations using the same set of modalities for prediction of all classes. In this work, we present a combined framework, cascaded multiview canonical correlation (CaMCCo), for fusion and cascaded classification that incorporates all diagnostic categories and optimizes classification by selectively combining a subset of modalities at each level of the cascade. CaMCCo is evaluated on a data cohort comprising 149 patients for whom neurophysiological, neuroimaging, proteomic and genomic data were available. Results suggest that fusion of select modalities for each classification task outperforms (mean AUC = 0.92) fusion of all modalities (mean AUC = 0.54) and individual modalities (mean AUC = 0.90, 0.53, 0.71, 0.73, 0.62, 0.68). In addition, CaMCCo outperforms all other multi-class classification methods for MCI prediction (PPV: 0.80 vs. 0.67, 0.63).

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Brief communication

Polygenic score prediction captures nearly all common genetic risk for Alzheimer's disease

Valentina Escott-Price [a,*], Maryam Shoai [b], Richard Pither [c], Julie Williams [a], John Hardy [b,**]

[a] Institute of Psychological Medicine and Clinical Neurosciences, MRC Centre for Neuropsychiatric Genetics & Genomics, Cardiff University, Cardiff, UK
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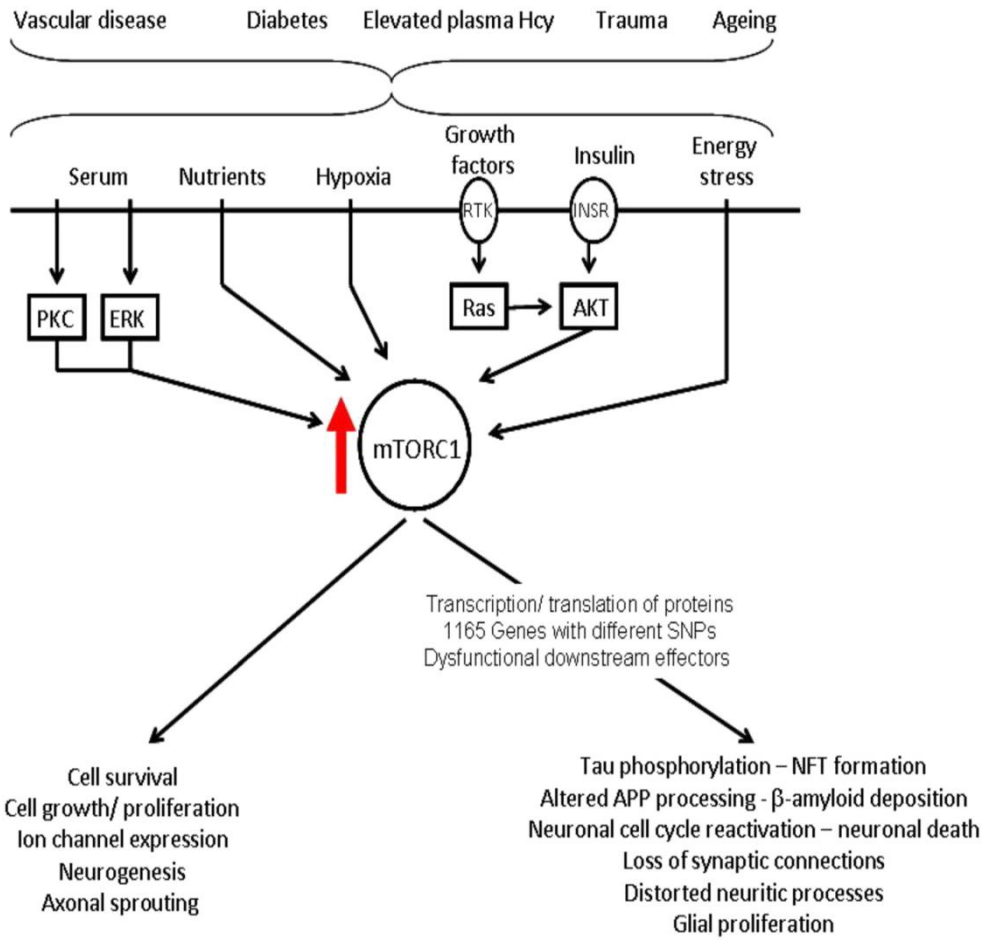
ABSTRACT

We estimate the maximum prediction accuracy for the risk of Alzheimer's disease based on disease prevalence and heritability of liability. We demonstrate that the recently reported AUC values for predicting of Alzheimer's disease using polygenic scores reach about 90% of the estimated maximum accuracy that can be achieved by predictors of genetic risk based on genomic profiles.

Novel approaches to polygenic risk score algorithms for AD: Dr Zsuza Nagy



Low mTOR pathway SNP burden = protection

High mTOR pathway SNP burden = risk

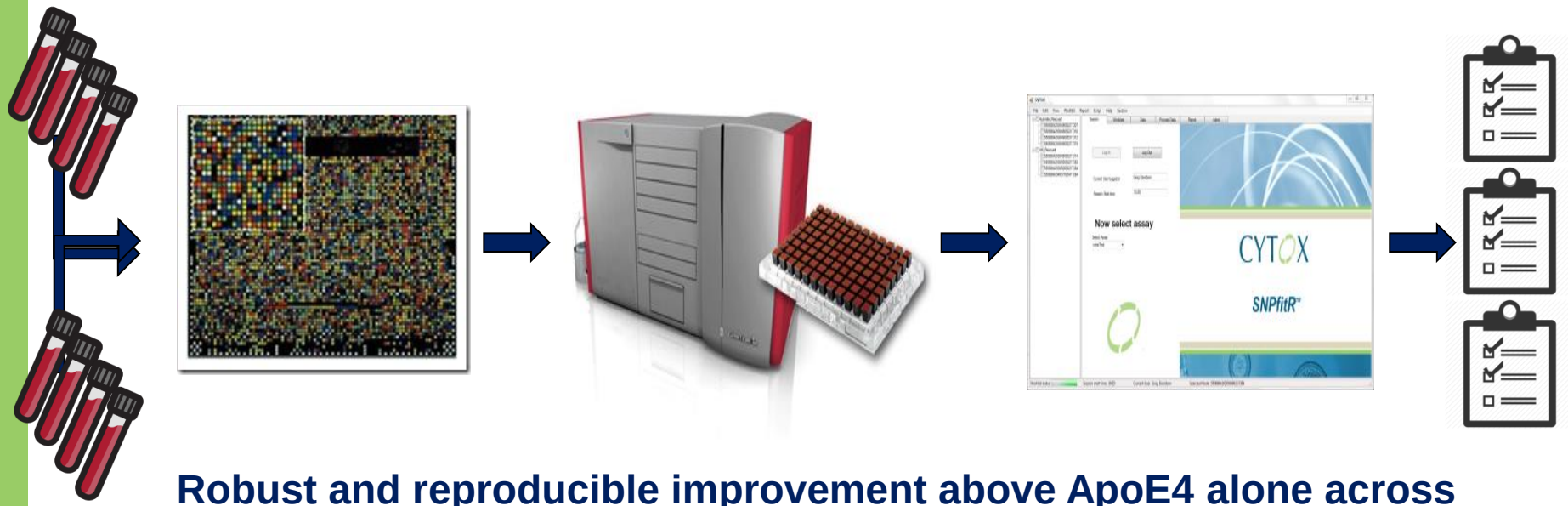
- mTOR pathway regulates the adaptive response of cells to their environment
- Activation/inhibition involves:
  - Large number of genes with
  - Many variations
- Theoretical modelling of the effects of SNPs on mTOR regulated pathways based on:
  - SNP effect on gene function (loss/gain function)
  - Allele number
  - Number of SNPs on same gene
  - Number of affected genes on the pathway
- ApoE-independent
- AUC: ~0.8
- Specificity and Sensitivity ~ 80%
- Three independent cohorts (Bham, AIBL, ADNI)

CYTOX

UNIVERSITY OF BIRMINGHAM

Offering a powerful service for genetic assessment and risk stratification

Providing a **fast**, **accurate**, **reliable** and **cost-effective** genetic testing solution from whole blood test for assessing Alzheimer's Disease risk



Robust and reproducible improvement above ApoE4 alone across broad populations, including different ethnicities

Standardised testing platform:

- Applied Biosystems™ Axiom™ Arrays on clinically proven GeneTitan™ Platform
- Cytox variaTECT™ SNP Array for genotyping
- Cytox SNPfitR™ Software for risk scoring
- Future CLIA approved tests for clinicians

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Core Lab network: geographic reach via high quality laboratories

Cytox Collaborative Opportunities: Pharma and Academia

- Level of performance of currently available PRS algorithms is consistent with potential utility for population stratification in clinical trials and development of companion diagnostics

- Opportunities for true collaborative partnerships in development and validation
  - Stratification of samples for clinical trials – savings in cost and time
  - Drug responder profiling – clinical trial optimisation
  - LDT and Companion Diagnostic approaches

- Multiple PRS algorithms already in place and being validated, providing different information to suit specific requirements: *amyloid status; clinical risk; drug response prediction; differential dementia diagnosis*
  - Offering high overall accuracy for prediction of amyloid status in research
  - Locked PRS algorithms for use in clinical trials
    - **University College London**
    - **University of Birmingham** (mTOR)
    - **University of Cardiff** (coming soon….)

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- UPenn — John Trojanowski, Virginia Lee, Vivianna Van Deerlin, David Irwin
- UCL Translational Imaging Group — Andre Altmann
- UCL Institute of Neurology — John Hardy
- University of Birmingham — Zsuzsa Nagy
- University of Cardiff — Valentina Escott-Price; Julie Williams
- Cytox — Greg Davidson (Ledcourt Associates)

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