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Maryam Shoai

APPLICATION OF POLYGENIC RISK SCORE IN IDENTIFICATION OF AMYLOID POSITIVE INDIVIDUALS

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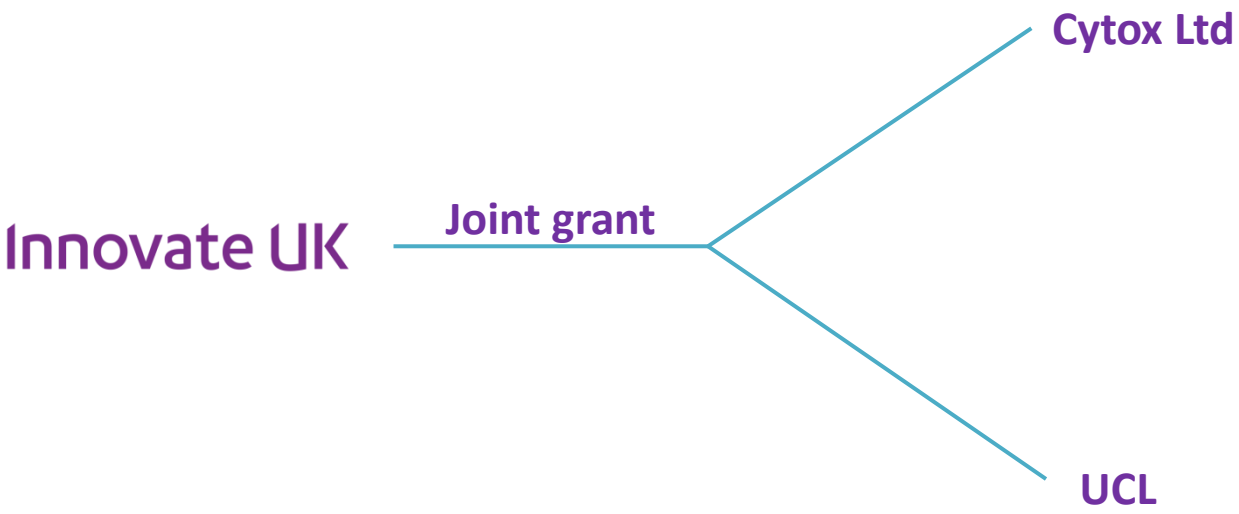
Conflicts of Interest



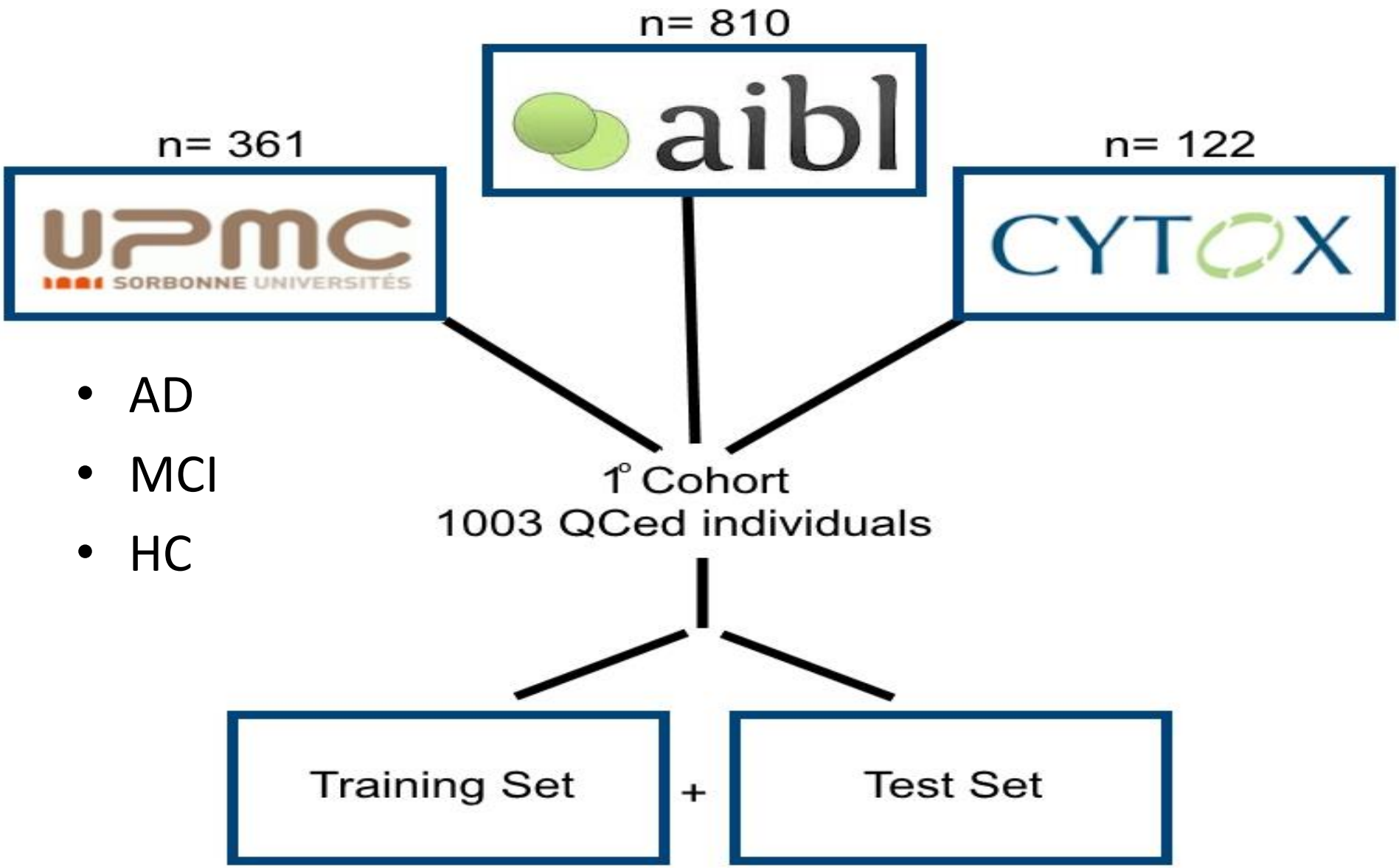
The need

- Identify Amyloid positive patients early on for use in clinical trials
- The ultimate promise of a measure that could identify those at higher risk of AD in mid life

Identify genetic biomarkers

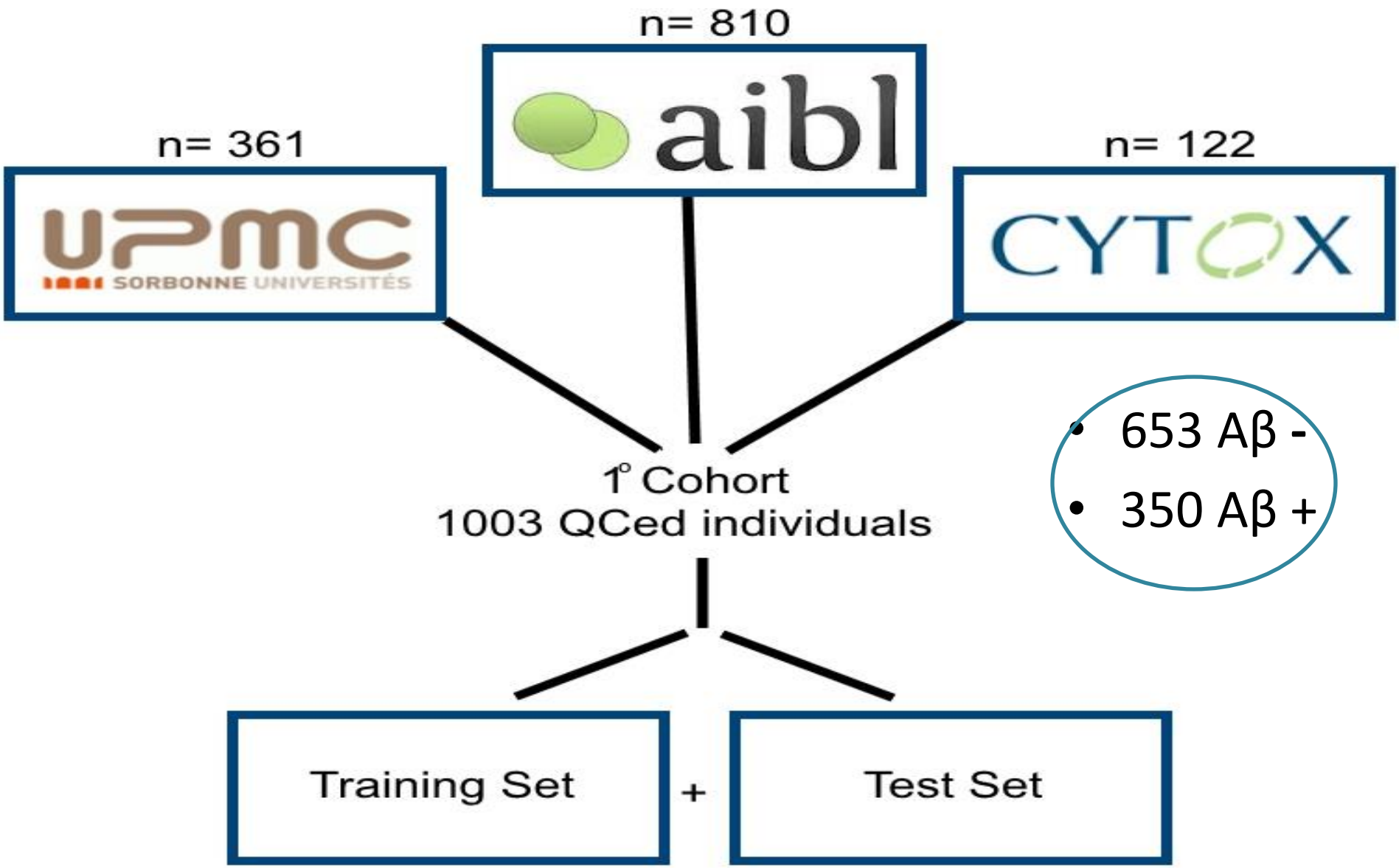
Cohort can not be contaminated with poorly characterized samples

The cohort

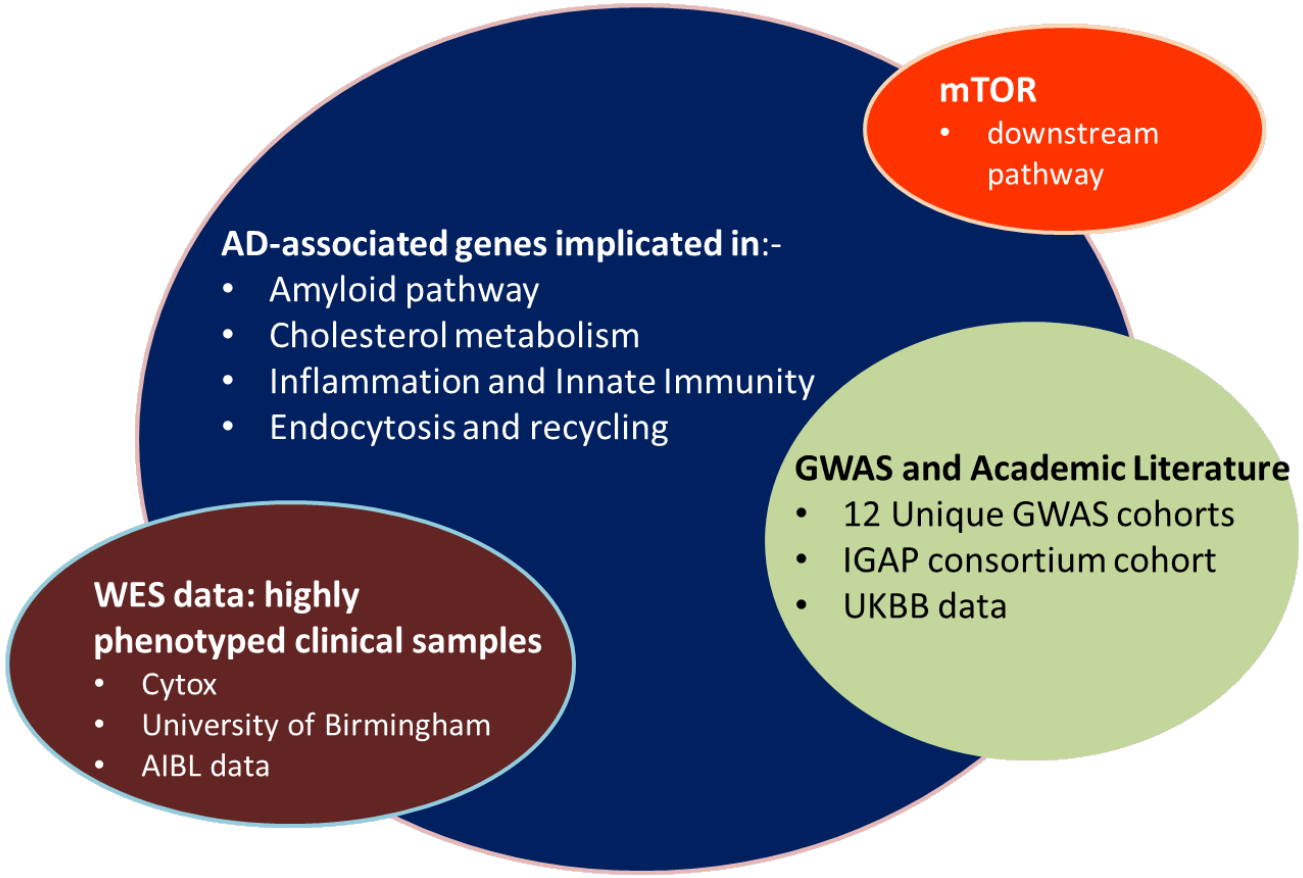


- AD
- MCI
- HC

The cohort


n= 810
aibl
n= 361
UPMC
SORBONNE UNIVERSITÉS
n= 122
CYTOX
1° Cohort
1003 QCed individuals
• 653 Aβ -
• 350 Aβ +
Training Set
+
Test Set

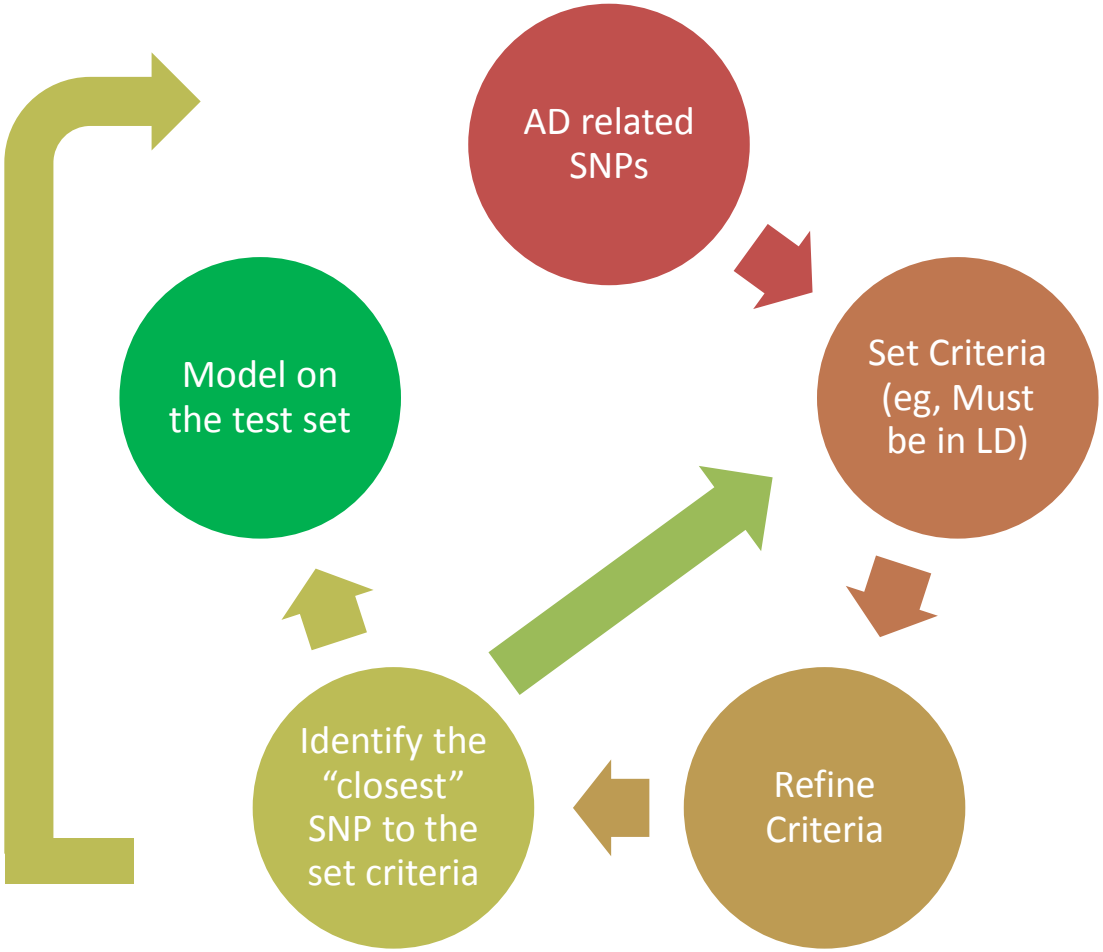
The *varia*TECT™ array: ~130k SNPs



Two approaches to modelling

affymetrix

Model 1- Hypothesis Driven



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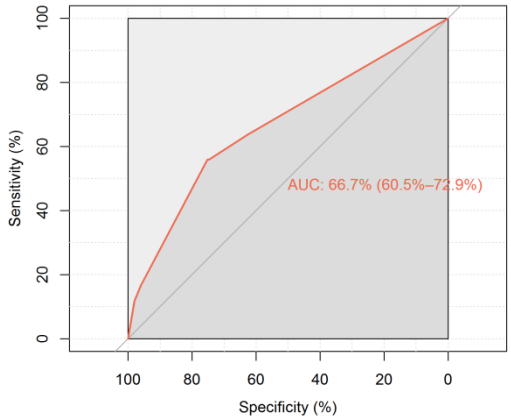
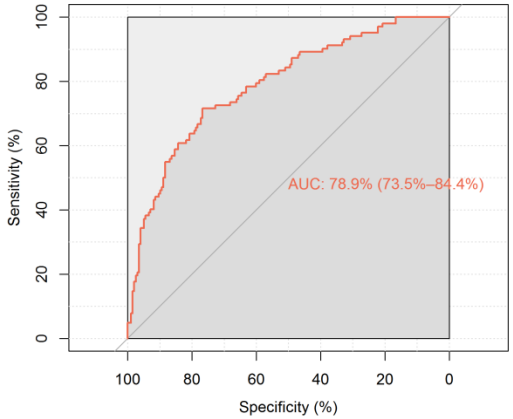
Model Performance on Amyloid +ve subjects with or without cognitive impairment

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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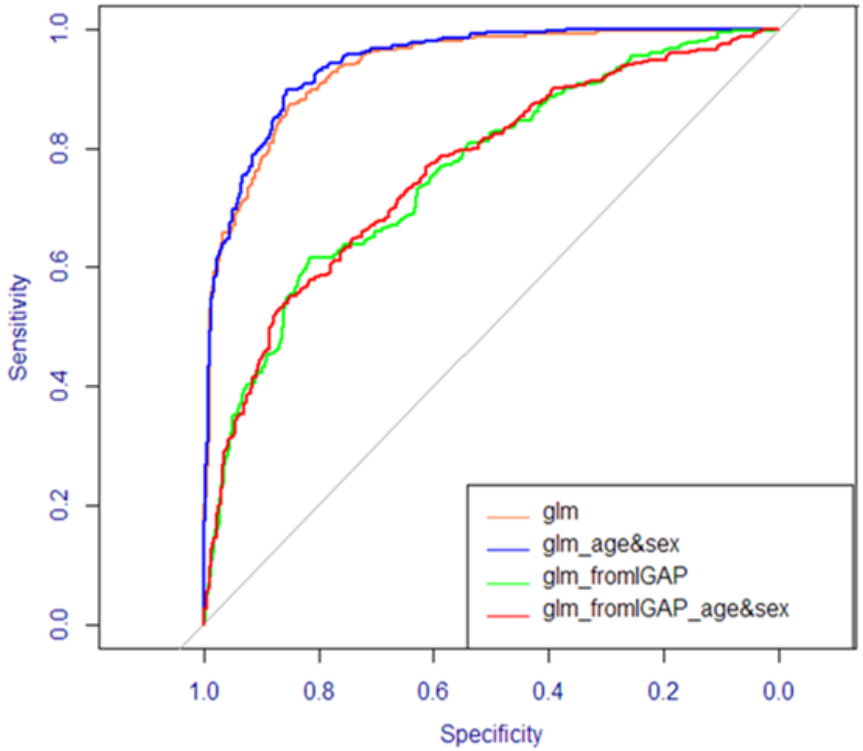
Model 2-Unbiased variable selection

- 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

Sample Characteristics

- AD cases:
  - Primary diagnosis of AD, secondary pathology can not be ALS, FTLD-TDP, DLB, PD
  - No familial cases with PSN mutation.
- Controls:
  - Unremarkable Adult brain with Braak and CERAD less than 1.
  - Clinical schizophrenia or non-normal cognition excluded.
- All age matched, over 65 and Caucasian.

Predict phenotype

- Sample's phenotype unknown to UCL
- Fit each person (n=270) – age, gender and weighted polygenic score
- Derive the probability of Amyloid deposits being present

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Predicting ability of the models

- All models run blind

	False positive rate	False negative Rate	True Positive rate	True Negative Rate
model1	52	17.788	82.212	48
model1+APOE	36	25.481	74.519	64
model1_on_IGAP	52	4.808	95.192	48
model1_on_IGAP+APOE	28	17.308	82.692	72
glmmodel	24	33.173	66.827	76
Combined_glmmodel_model1	28	31.250	68.750	72

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Post unblinding

name	NSNPs	PPV_33	NPV_33	PPV_50	NPV_50
model1	20	75.81%	34.14%	60.69%	51.28%
model1+APOE	22	88.66%	36.86%	79.38%	54.23%
model1_on_IGAP	18	91.06%	37.70%	83.38%	55.13%
model1_on_IGAP+APOE	20	95.78%	41.22%	91.79%	58.74%
glmmodel	141	91.51%	37.98%	84.15%	55.43%
Combined_glmmodel_model1	158	88.66%	36.86%	79.38%	54.23%
age+sex	none	89.02%	37.01%	-	-
APOE	2	94.58%	37.55%	-	-
age+sex+APOE	2	91.51%	37.98%	-	-

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In summary…

- Two basic models: Hypothesis and Hypothesis-free variant selection.
- Blind validation of models:
  - True Positive Rate around 90% or greater
  - True Negative Rate around 70% is possible
- Models yield results better than what is currently available in both APOE4 negative cohorts and a mixed cohort
- Level of performance consistent with potential utility in population stratification in clinical trials

Thank you

- AIBL Simon Laws, Colin Masters, Larry Ward
- INSIGHT Harald Hampel, Bruno Dubois, Simone Lista
- KU Leuven Rik Vandenberghe, Isabelle Cleynen
- UPenn John Trojanowski, Virginia Lee, Vivianna Van Deerlin, David Irwin

- UCL Translational Imaging Group Andre Altmann

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Thank you

John Hardy

Richard Pither

Valentina Escott-Price

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