CYTOX

# A New Genetic Test for Alzheimer's Disease and Dementia Risk – *with transformational potential*

# A Polygenic Risk Score test for Alzheimer's Disease

## *varia*TECT™ and SNPfitR™ provide an accurate genetic blood test for the assessment of Alzheimer's Disease risk


**Best in class genotyping platform with one software solution offering two analysis options for amyloid PET positivity:-**

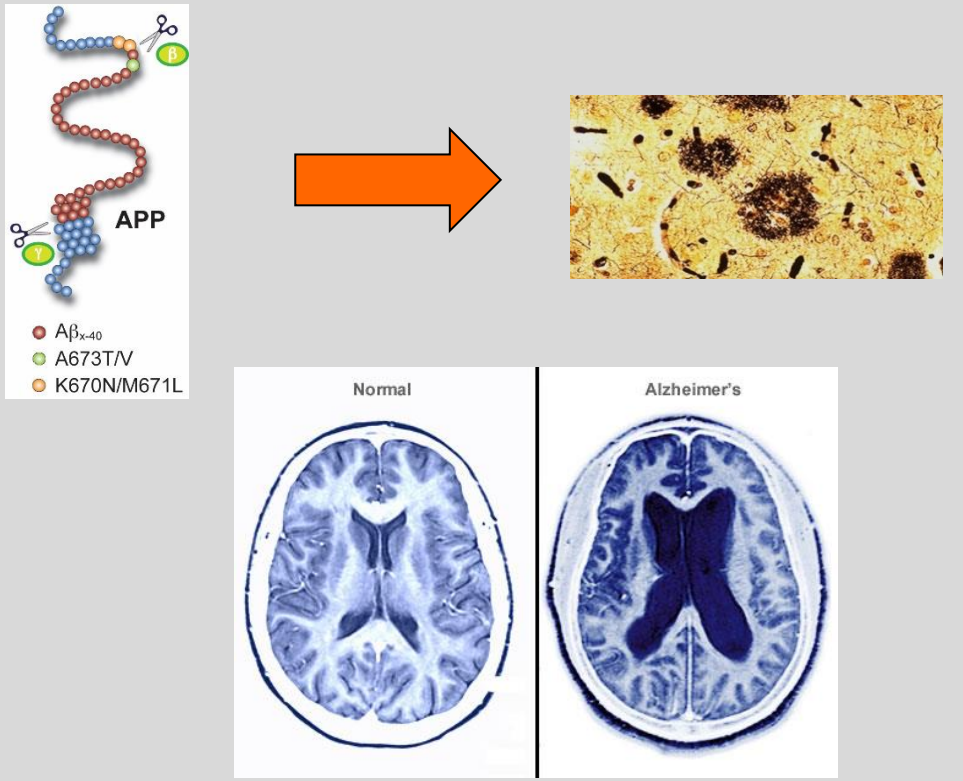
1. **Assist Pharma in stratifying trial subjects**
2. **Support academic research**
3. **Clinical test for physicians**

**95%**
**Amyloid Positive Predictive Value**

CYTOX

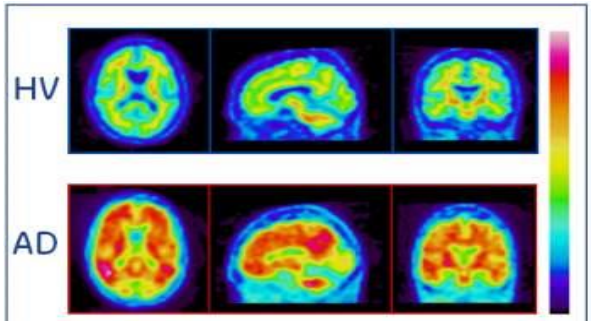
# Biomarkers are crucial to the early identification of Alzheimer's Disease

***"Genetic analysis is the most effective way of deciding who should be assessed for early disease"***
**– Professor John Hardy**



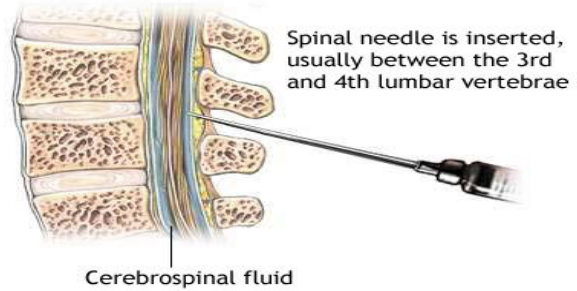

**<u>Detection of early changes is key</u>: Working at the molecular level**

- **PET Imaging: Very expensive and limited availability**
- **Lumbar Puncture: Invasive and high risk; limited reproducibility**




**Brain Amyloid Imaging**

**PET – Positron Emission Tomography**




**Lumbar Puncture**

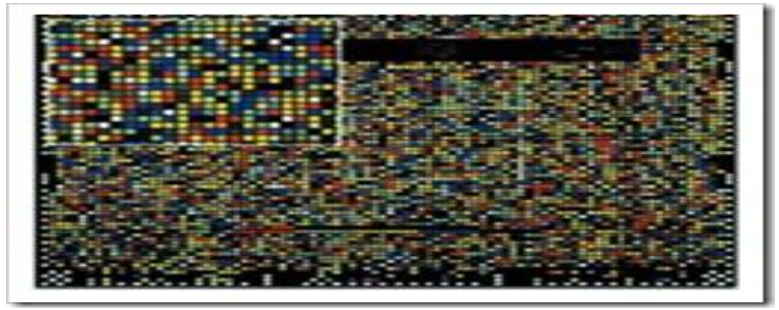
**CSF – amyloid and tau fragments**

CYTOX

# Genetic building block strategy: Polygenic Risk Score

A polygenic risk score (PRS) algorithm is a sum of genetic risk

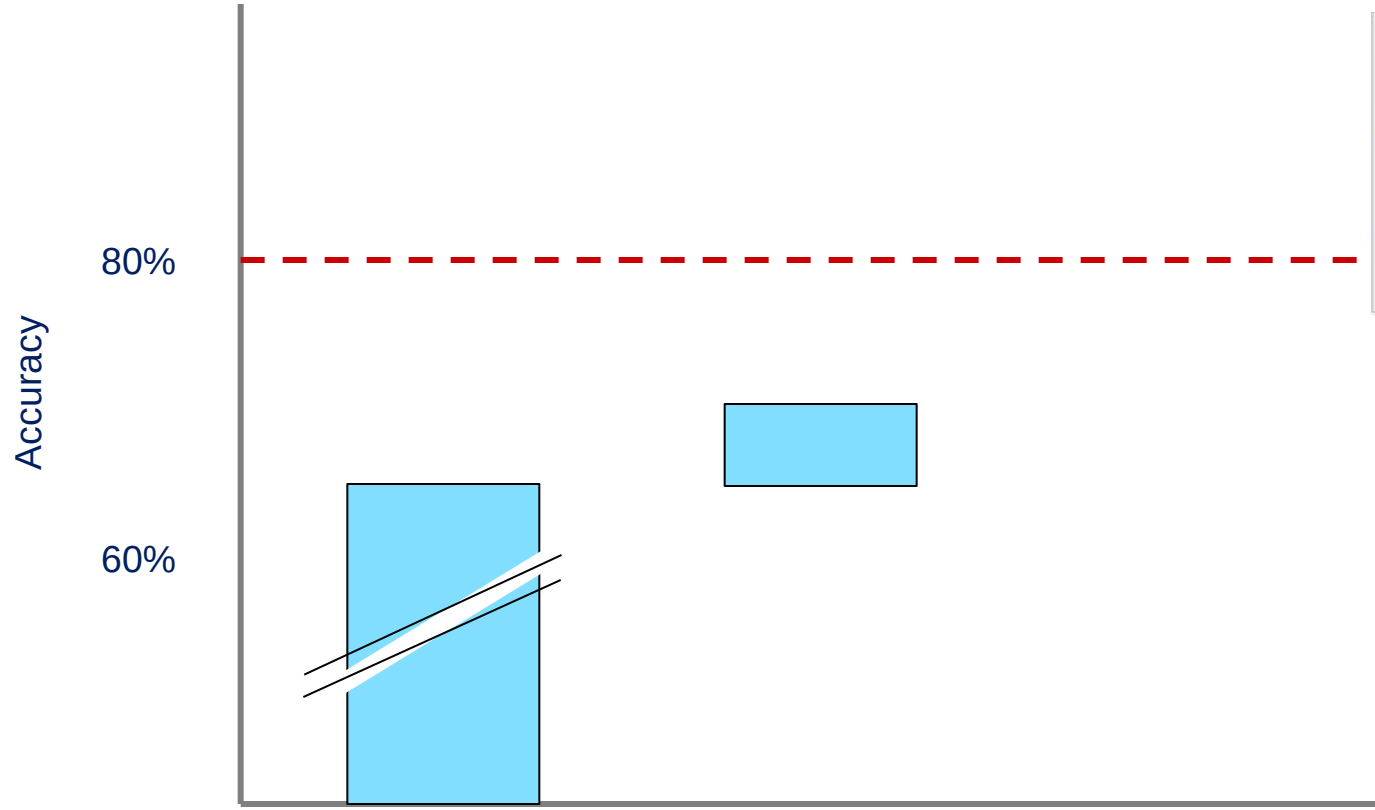
1. Comprehensive AD SNP genotyping array
2. Amyloid stratification PRS algorithm
3. *geno*TOR PRS algorithm for identification of clinical AD risk



*varia*TECT™

SNPfitR™

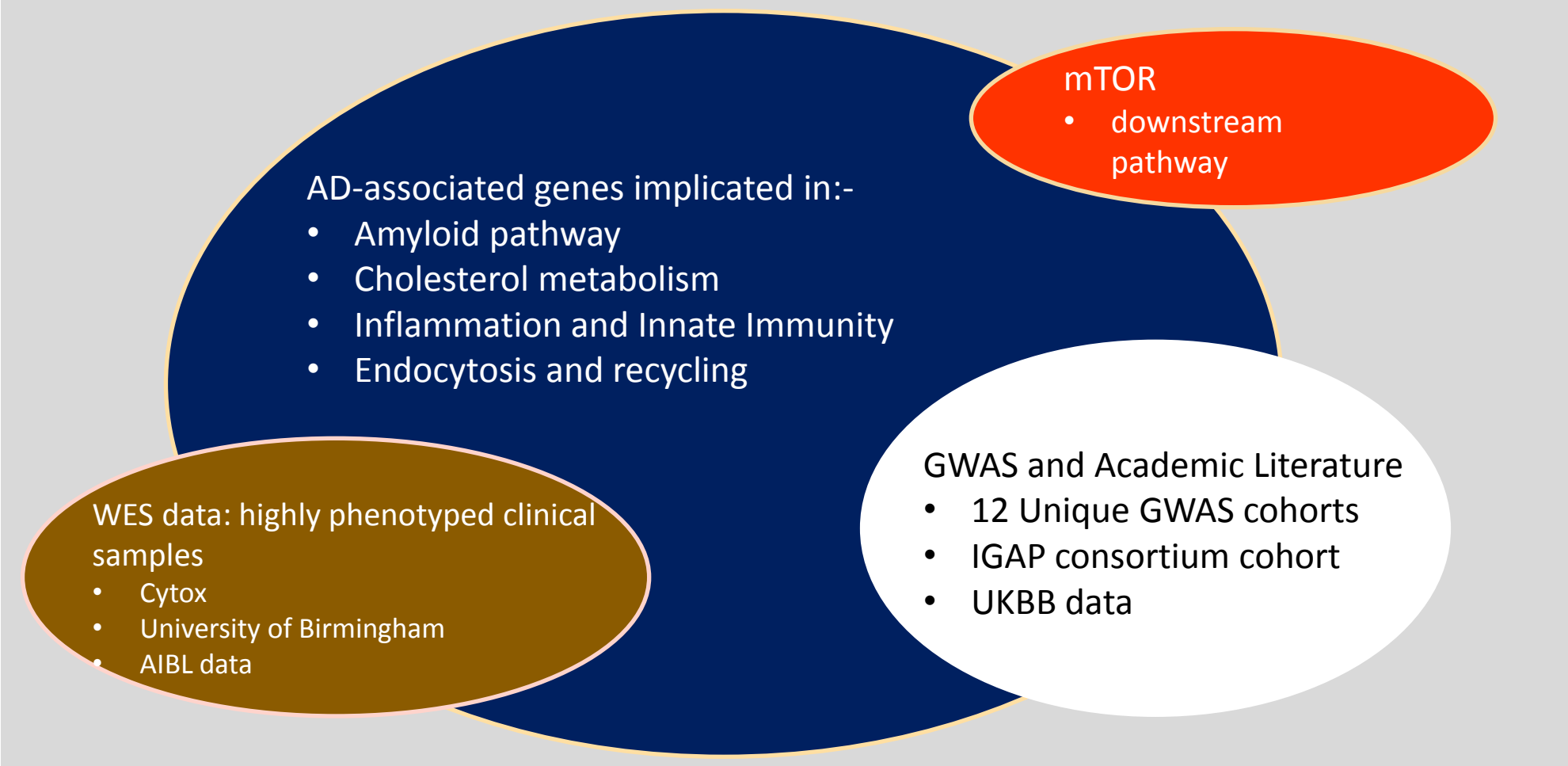
affymetrix




CYTOX

# The *varia*TECT™ SNP array: ~130,000 SNPs

The *varia*TECT™ panel is the most comprehensive panel available for the detection of Alzheimer's Disease informative SNPs, comprising novel and known variants in genes pertaining to pathways implicated in Alzheimer Disease aetiology




CYTOX

affymetrix

# Polygenic Risk Score (PRS): modelling and validation

- Two basic models:-
  - **Hypothesis-driven variant selection (Model 1)**
  - **Hypothesis-free variant selection (Model 2)**

- All PRS models trained in PET-amyloid (or CSF) – confirmed cases and controls

- Blind validation of models in clinically assessed, post-mortem, pathology-confirmed cases and controls

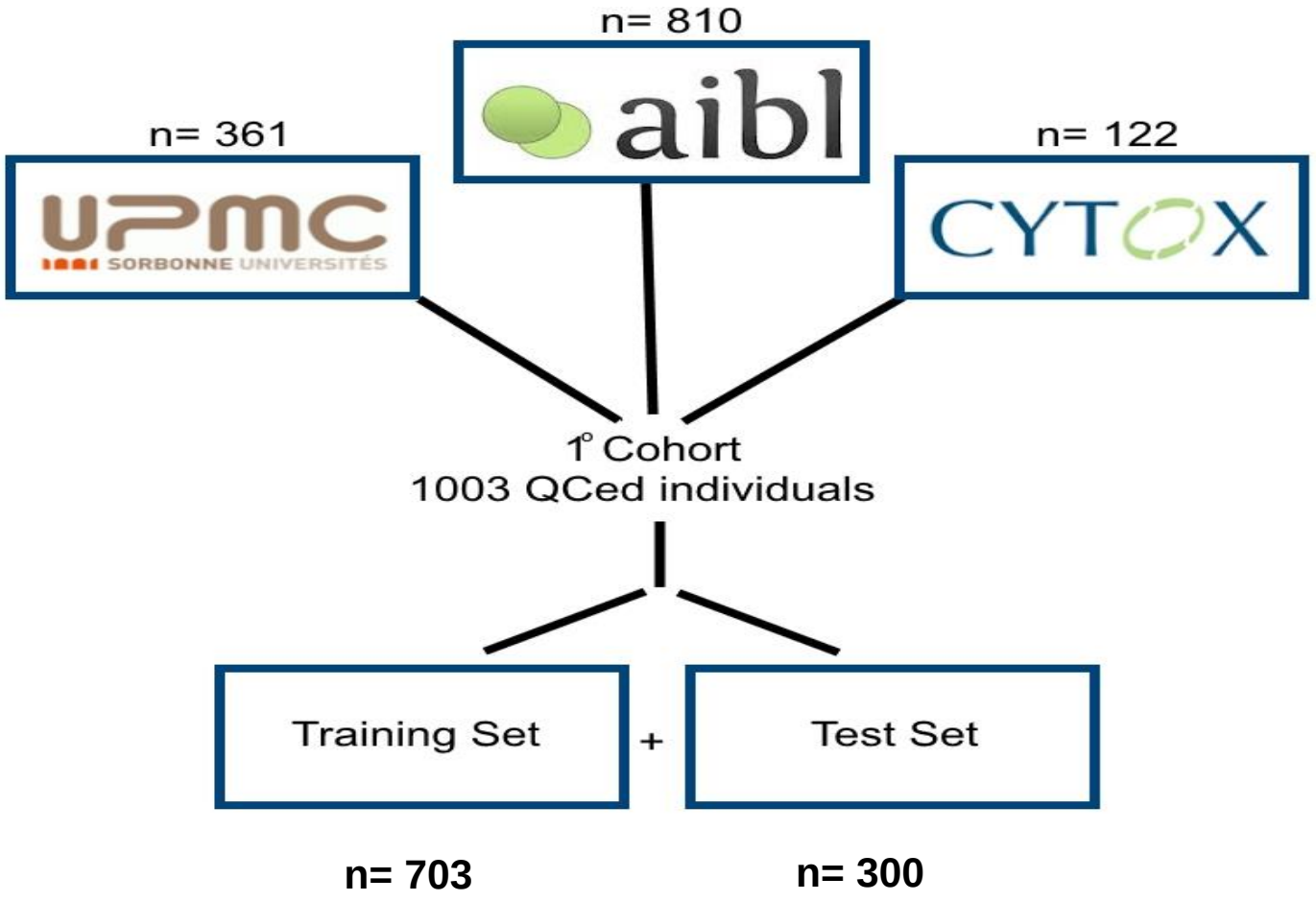
**Training and test clinical samples**:-

- AIBL Simon Laws, Colin Masters, Larry Ward
- INSIGHT Harald Hampel, Bruno Dubois, Simone Lista
- KU Leuven Rik Vandenberghe, Isabelle Cleynen

**Validation Samples**:-

- UPenn (Brain Bank) John Trojanowski, Virginia Lee, Vivianna Van Deerlin, David Irwin

# Training set description

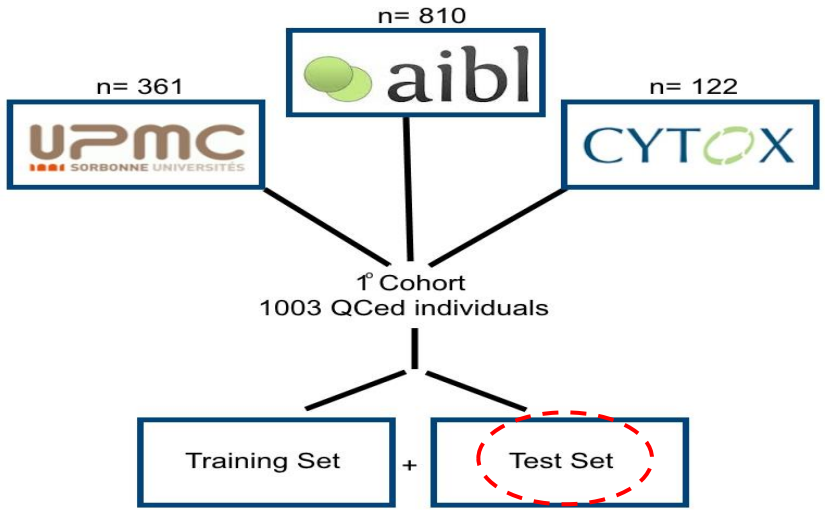



| | |
|---|---|
| Age (mean) | 72.82 |
| Age (range) | 55-93 |
| Method of amyloid analysis | PET/CSF |
| Sample Size | 703 |
| Gender ratio M:F | 296:407 |
| Ethnicity | Caucasian |

| | |
|---|---|
| % Amyloid +ve | 35% |
| ApoE4 carrier | 31% |
| ***Clinical Diagnosis*** | |
| - Cognitively Normal | 76% |
| - MCI | 9% |
| - Alzheimer's Disease | 15% |

# Test set results

| | |
|---|---|
| Sample Size | **300** |
| % Amyloid +ve | 34% |
| ApoE4 carrier | 35% |
| ***Clinical Diagnosis*** | |
| - Cognitively Normal | 71% |
| - MCI | 12% |
| - Alzheimer's Disease | 17% |




| Model name | Sensitivity | Specificity | **AUC** | PPV_33 | NPV_33 |
|---|---|---|---|---|---|
| 1 | 72.55% | 72.73% | **78.93%** | 80.12% | 63.62%` |
| 2 | 86.29% | 86.22% | **94.35%** | 89.07% | 82.85% |

# Validation test set results

***Pathology Confirmed Samples from UPenn (blinded analysis results)***

| | |
|---|---|
| Sample Size | **237** |
| % Amyloid +ve | 88% |
| ApoE4 carrier | 50% |
| ***Clinical Diagnosis*** | |
| - Cognitively Normal | 30% |
| - MCI | 4% |
| - Alzheimer's Disease | 53% |
| - Other dementia | 13% |

| Model | Sensitivity | Specificity | AUC | **PPV33** | NPV33 |
|---|---|---|---|---|---|
| 1 | 0.80 | 0.80 | 85.55% | **95.78%** | 41.22% |
| 2 | 0.72 | 0.72 | 75.12% | **91.51%** | 37.98% |

| Model name | False positive rate | False negative Rate | **True Positive rate** | True Negative Rate |
|---|---|---|---|---|
| 1 | 52 | 4.808 | **95.192** | 48 |
| 2 | 24 | 33.173 | **66.827** | 76 |

CYTOX

# Conclusions – presented at AD/PD Conference (Vienna, March 2017)

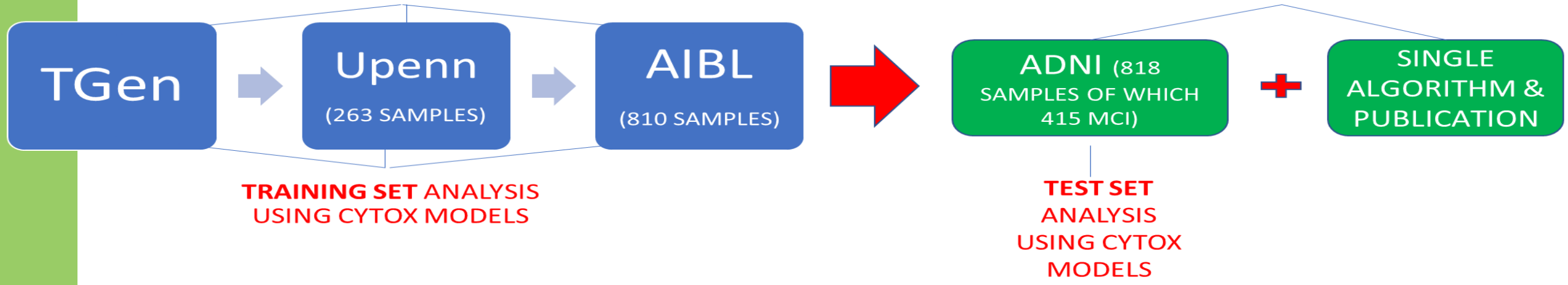
- Two basic models: Hypothesis-driven and Hypothesis-free variant selection

- Blind validation of models:-
  - True Positive Rate of 95% or greater
  - True Negative Rate around 76% is possible

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

**Level of performance consistent with potential utility in population stratification in clinical trials**

# Ongoing optimisation of PRS amyloid algorithms in MCI cohorts




**PRS Algorithm locked for CLIA/LDT verification and validation:**

- **Research version available for collaboration today**
- **PRS Algorithm lock: 3Q 2017**
- **RUO Assay in CLIA-compliant lab: 4Q 2017**

# Collaborative opportunities

- Multiple PRS algorithms offering high overall accuracy for prediction of amyloid status
- Word-class scientific team
- Opportunities for true collaborative partnerships

1. Stratification for clinical trials – savings in cost and time
2. Drug responder profiling – clinical trial optimisation
3. Companion Diagnostic approaches

*Next steps…*

# Genetics and Alzheimer's Disease Expertise

## Experienced Management Team

**Dr Andrew Carr (Chairman)**
- GE Healthcare; Thermo Fisher; Teraview; deltaDOT; Akubio

**Dr Richard Pither (CEO)**
- GE Healthcare; Lorantis; UCB-Celltech – Alzheimer's

**Dr Kevin Banks (Business Strategy and Marketing)**
- ADI; Affymetrix – Genetic assay platforms

**Dr Alex Gibson (Business Development)**
- GE Healthcare Business Development – Alzheimer's

**Dr Jonathan Wilde (Clinical Product Development)**
- Veracyte; Astra-Zeneca – Genetic products

**Dr Greg Davidson (Software Engineering and Regulatory)**
- Quotient Diagnostics – regulated software

## World-Class Scientific Partners

**Prof John Hardy**
- Chair of Molecular Biology of Neurological Disease at the UCL Institute of Neurology

**Dr Maryam Shoai**
- Post-doctoral Expert in Genetic Statistics, UCL Institute of Neurology

**Dr Zsuzsa Nagy**
- Institute of Inflammation and Ageing, University of Birmingham

**Profs Colin Masters, Simon Laws, Ian Cooke**
- AIBL (The Australian Imaging, Biomarker & Lifestyle Flagship Study of Ageing)

**Profs Harald Hampel and Bruno Dubois**
- Neurological Institute of the University Salpêtrière Hospital in Paris, UPMC

**Profs Rik Vandenberghe and Isabelle Cleynen**
- Research Group Experimental Neurology, KU, Leuven

**Profs John Trojanowski, Vivianna Van Deerlin and Virginia Lee**
- University Pennsylvania