# DISEASE PROGRESSION MODELLING

## Quantitative disease diagnosis and prognosis

POND group: http://pond.cs.ucl.ac.uk, part of the Centre for Medical Image Computing: http://www.ucl.ac.uk/cmic

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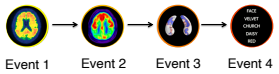
**Progressive diseases present numerous challenges:**

- Long duration and pre-symptomatic phase – no single biomarker is dynamic throughout
- Complex, overlapping phenotypes – complicates differential diagnosis
- Subtypes and variation between groups and individuals – heterogeneity in clinical trials

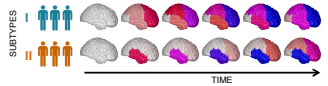
Disease progression modelling builds **quantitative biomarker signatures** for diagnosis, prognosis, and predicting response to treatment

## METHODS



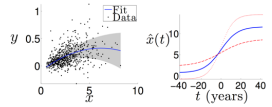

### Event-based model

- Estimates the sequence in which different biomarkers become abnormal [1, 2]
- Incorporates multi-modal information
- Provides probabilistic patient staging



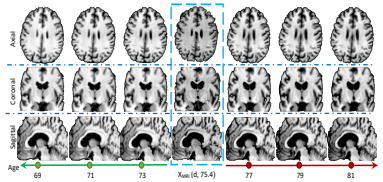

### Subtype and Stage Inference

- Reconstructs the subtypes and stages of a disease from cross-sectional data [3]
- Identifies novel disease phenotypes
- Provides subtyping and staging information



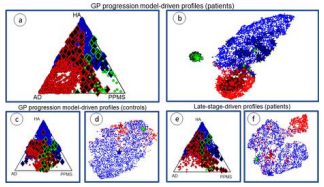

### Differential equation model

- Estimates trajectories from short-term data [4]
- Quantifies the time it takes for a biomarker to become abnormal
- Gives prognostic information




### Degenerative Adversarial Neural Network

- Generate realistic brain images that mimic neurodegeneration [5]
- Generate ground truth for validating progression models
- Predict patients' outcomes




### Mechanistic Models

- Topological profiles [6] reveal that unique combinations of mechanisms characterise progression of different diseases
- Causal models for mechanistic understanding of drug action, e.g., in Multiple Sclerosis [7]
- Quantify tractography uncertainties for improved models

## ELECTRONIC HEALTH RECORDS and DIGITAL BIOMARKERS

### Electronic Health Records (EHR)

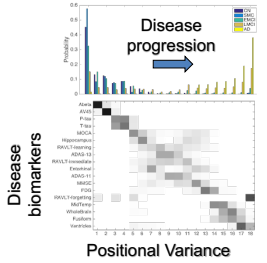
- Use EHR to model progression of multi-morbidity (co-occurrence of multiple chronic conditions) [8]
- Discovering subtypes of Alzheimer's Disease through clustering methods [9, 10]

### Digital biomarkers

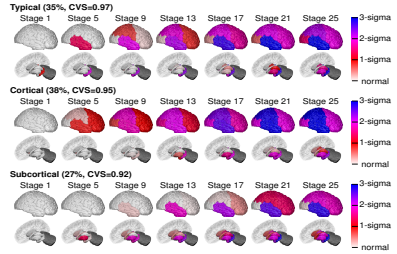
- Eye-tracking data-mining for augmenting cognitive assessment with instruction-less computerised tests [11]

## DISEASE APPLICATIONS

### Sporadic Alzheimer's disease

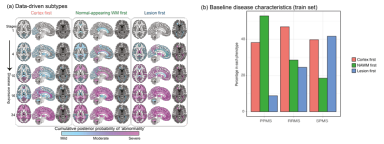



- More fine-grained disease staging using the event-based model [2]



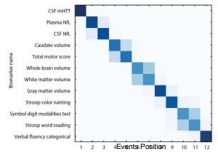

- Uncovering data-driven disease subtypes and their temporal complexity using Subtype and Stage Inference [3]

### Multiple sclerosis



- Redefining subtypes of MS using SuStaIn [12]
- Data-driven subtypes better predict treatment response and clinical progression

### Huntington's disease




- EBM of biofluid, imaging and clinical markers in Huntington's disease [13]
- Predicts for first time that biofluid markers change before imaging and clinical markers

## TRANSLATION: DATA-DRIVEN MEDICINE

### Clinical Tools

- Disease monitoring tool for clinical practice [14]
- Commercialisation for clinical trials applications

**REFERENCES**
[1] **Fonteijn** et al., Neuroimage 2012; [2] **Young** et al., Brain 2014; [3] **Young** et al., Nature Comm. 2018; [4] **Oxtoby** et al. Brain 2018; [5] **Ravi** et al., MICCAI 2019; [6] **Garbarino** et al., eLife 2019; [7] **Eshaghi** et al., PNAS 2018; [8] **Planell-Morell** et al., *Under review* MIE 2020; [9] **N. Alexander** et al., AAIC 2019; [10] **N. Alexander** et al., *Under review* MIE 2020; [11] **Mengoudi** et al., *Under review* JBHI 2019; [12] **Eshaghi** et al., medRxiv 2019; [13] **Wijeratne** et al., *Ann. Clin. Trans. Neurol.* 2018; [14] **Bellio** et al., AAIC 2019.

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# TADPOLE Challenge:

## big(-ish) data for predicting Alzheimer's disease progression

| | |
|---|---|
| Website: | tadpole.grand-challenge.org/ |
| Design paper: | arxiv:1805.03909 |
| Results paper: | arxiv:2002.03419 |


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EuroPOND

# Big Data (sharing) in Dementia

www.gaaindata.org

# Big Data (sharing) in Dementia

GAAIN
alzheimer's association
The Global Alzheimer's Association Interactive Network

USC Laboratory of Neuro Imaging
LONI
Laboratory of Neuro Imaging

ALZHEIMER'S DISEASE
ADCS
COOPERATIVE STUDY

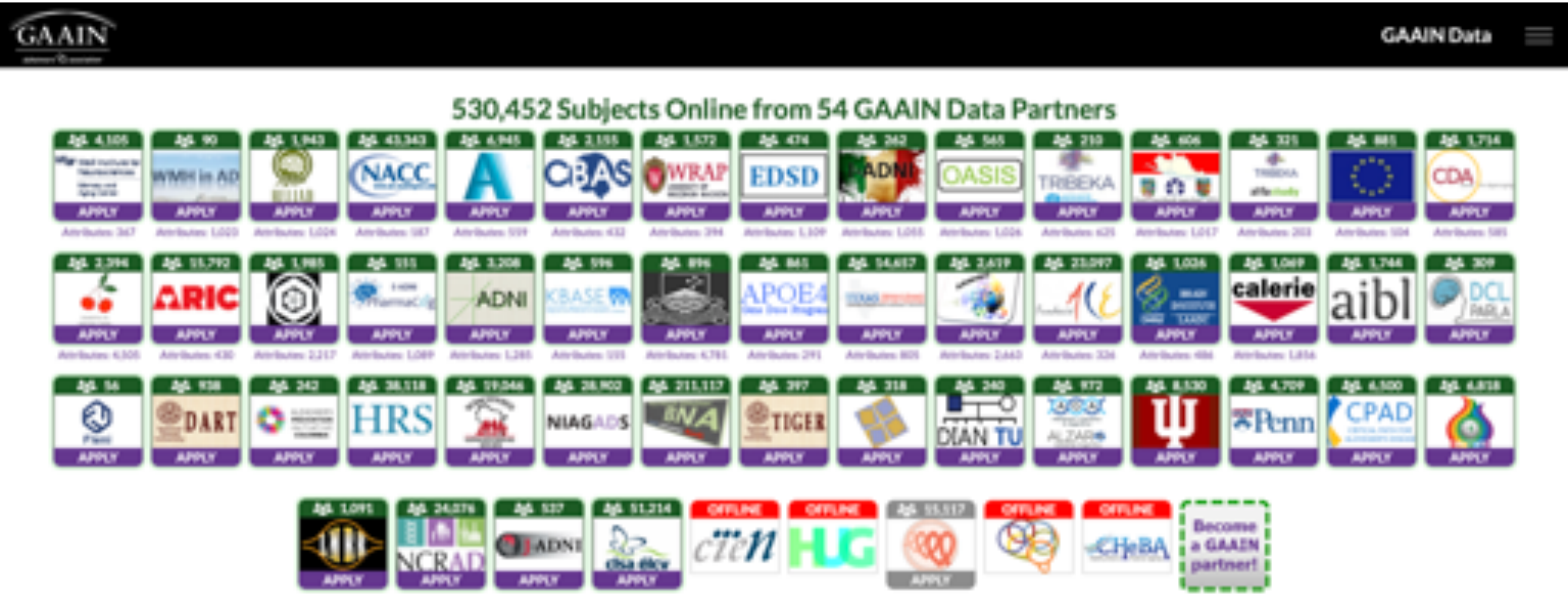
TRACKHD

Dementias Platform UK
Medical Research Council

PDBP

www.gaaindata.org

# Big Data (sharing) in Dementia



ADNI
Alzheimer's Disease Neuroimaging Initiative

ABOUT | STUDY DESIGN | DATA & SAMPLES | METHODS & TOOLS | DOCUMENTS | NEWS & PUBLICATIONS

HELP / FAQ | CONTACT

# PUBLICATIONS

ADNI publication pdfs can be searched by author, keyword, or PMCID using the ADNI PDF search above.

Filter results by:

Year Range:

from - to

nal

1800 Total Publications

**Patch-Based Label Fusion with Structured Discriminant Embedding for Hippocampus Segmentation**
Y. Wang, G. Ma, X. Wu and J. Zhou
2018; Journal Neuroinformatics; AWUW5r2FdzjauPDbjhuy doi:10.1007/s12021-018-9364-2

**Reduced brain amyloid burden in elderly patients with narcolepsy type 1**

# The Alzheimer's Disease Prediction Of Longitudinal Evolution challenge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Esther Bron,
Stefan Klein

Art Toga

UCL pond
Progression Of Neurodegenerative Disease

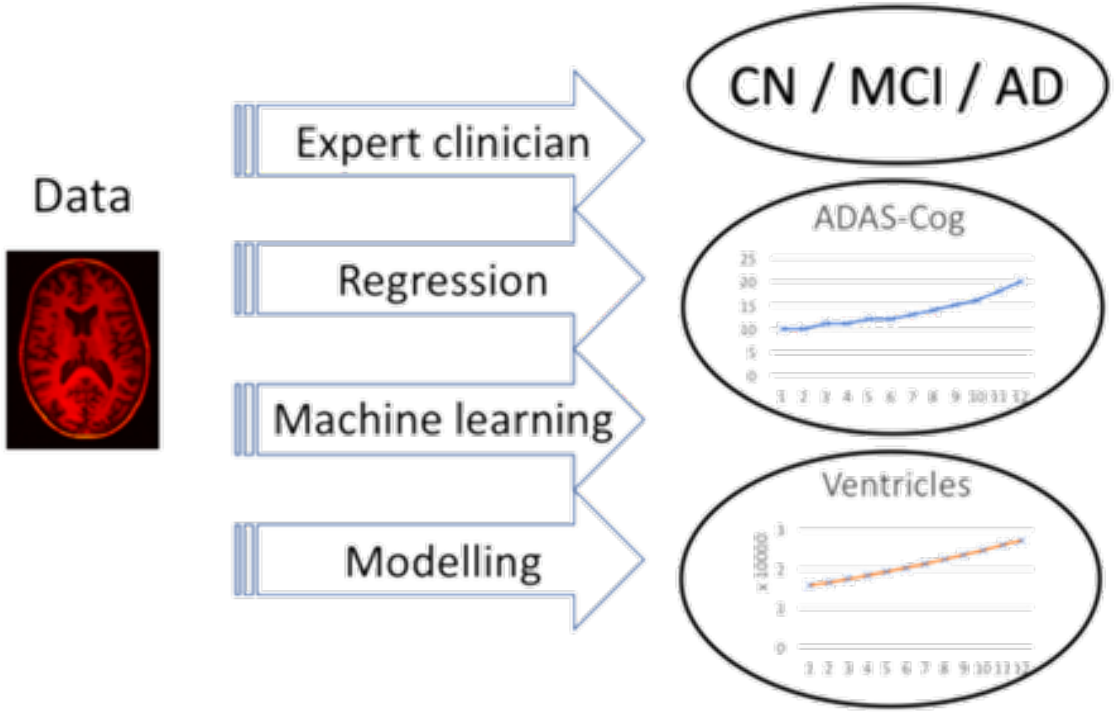
BIGR
Biomedical Imaging Group Rotterdam

ADNI

EuroPOND

# TADPOLE Overview

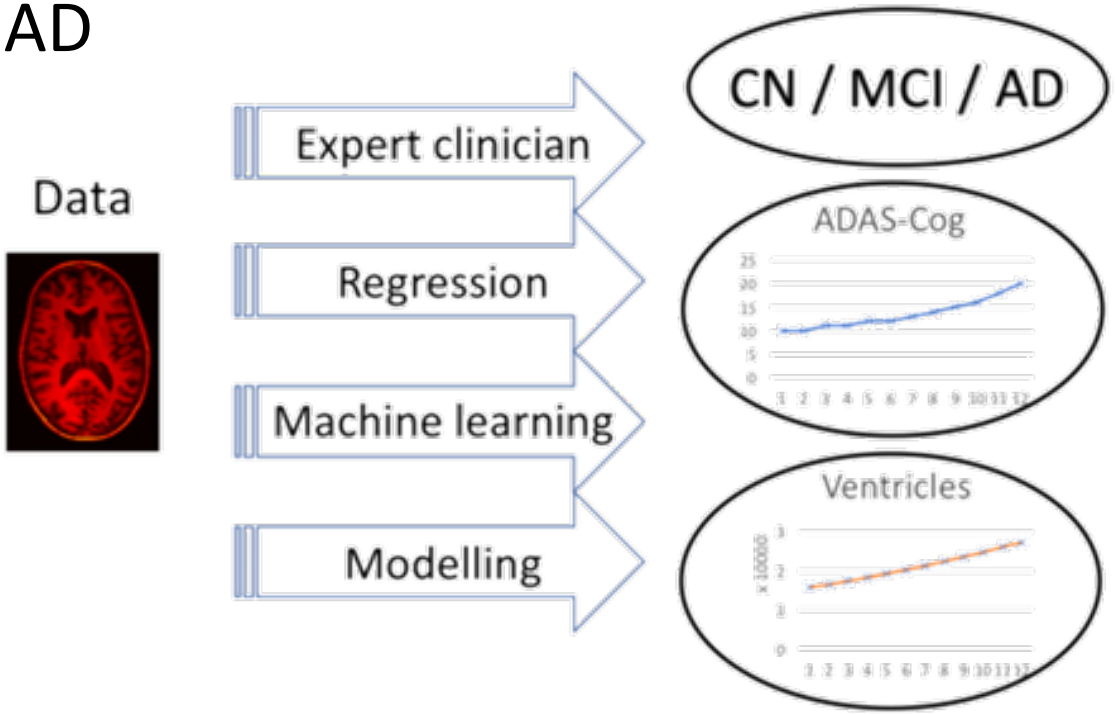
- A challenge to predict progression of individuals at risk of AD.
- Identify people that will develop AD over the next 1-5 years.
- ADNI provide data on up to 900 “rollover” subjects.
- TADPOLE stores forecasts and evaluates on follow-up data.



# About the challenge

1. How predictable is progression to AD in at-risk individuals?

2. How to best predict outcomes?
   - Data: longitudinal, X-sectional, MRI/DTI/etc.
   - Processing pipelines
   - Predictive models: man vs machine




3. Can we use these to improve cohort selection in clinical trials?

tadpole.grand-challenge.org

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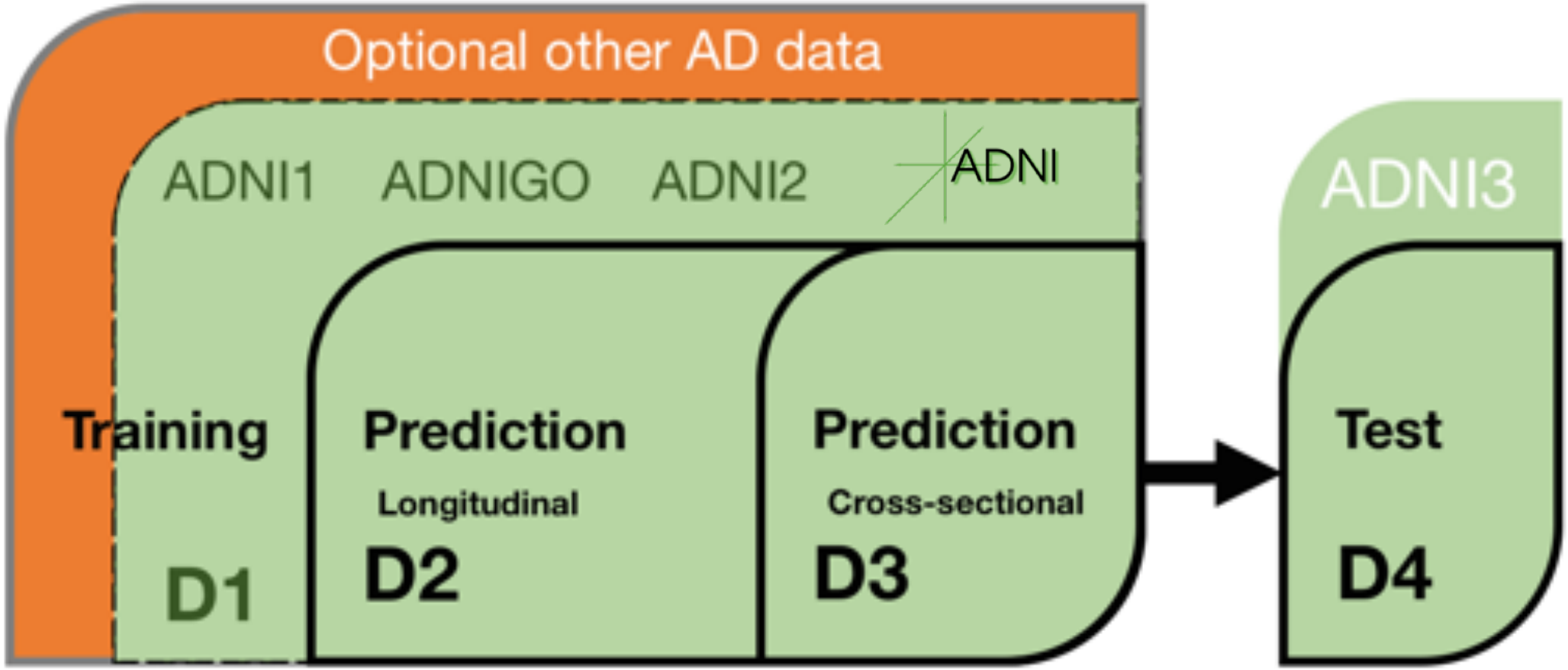
# About the challenge: how it works

- Predict future data for ADNI 3 “rollovers”
- Must outperform benchmark models

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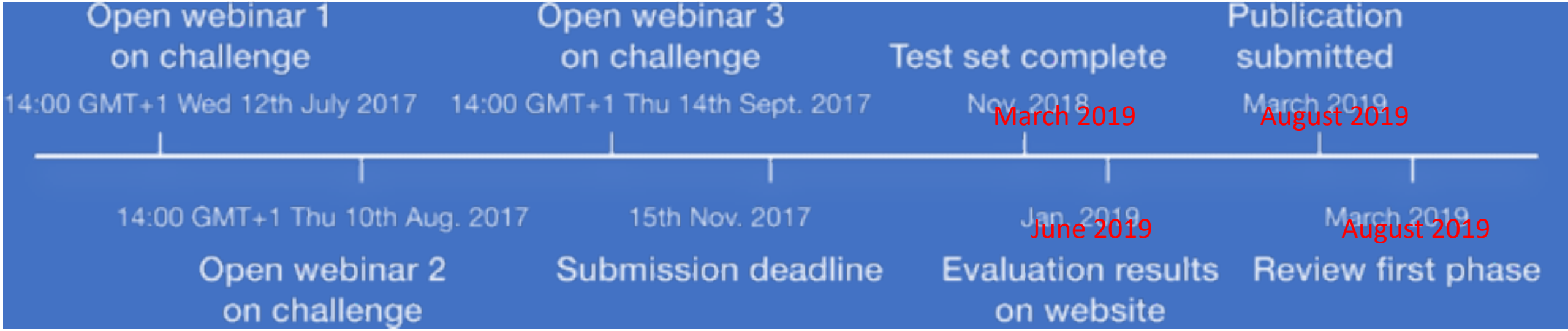
# Timeline


Open webinar 1
on challenge
14:00 GMT+1 Wed 12th July 2017
Open webinar 3
on challenge
14:00 GMT+1 Thu 14th Sept. 2017
Test set complete
Nov. 2018
March 2019
Publication
submitted
March 2019
August 2019
14:00 GMT+1 Thu 10th Aug. 2017
Open webinar 2
on challenge
15th Nov. 2017
Submission deadline
Jan. 2019
June 2019
Evaluation results
on website
March 2019
August 2019
Review first phase

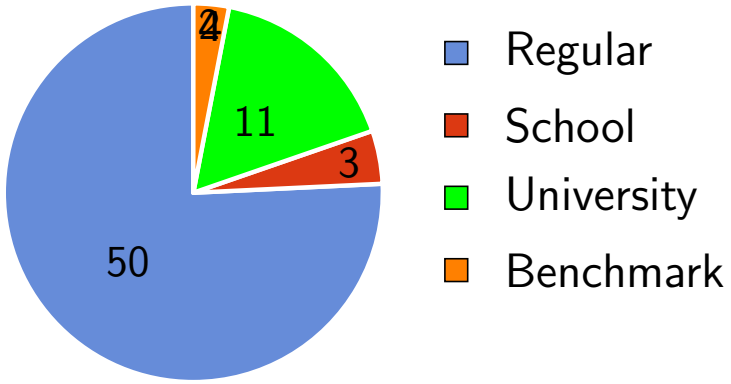
# Categories and Prizes

- Thank you to our sponsors
- 30K (GBP) to award.

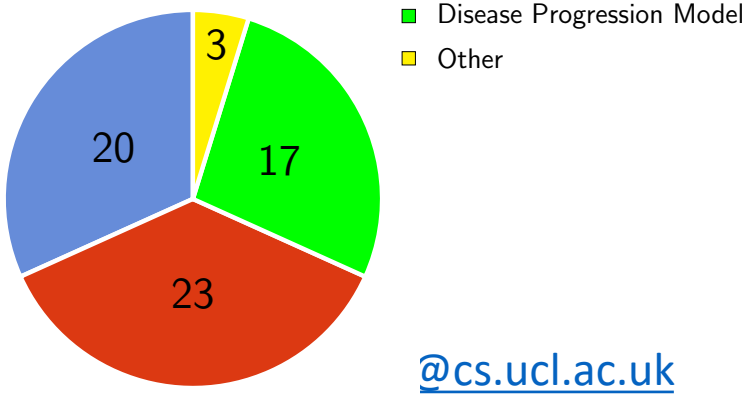
- £5K prize for clinical status
- £5K prize for ventricle volume
- £5K prize for ADAS13
- £5K prize for overall performance – **the TADPOLE champion**
- £5K prize for best student entry (clinical status)
- £5K prize for best high-school entry (clinical status)

# Submission statistics

Breakdown by number of entries




Breakdown by number of entries

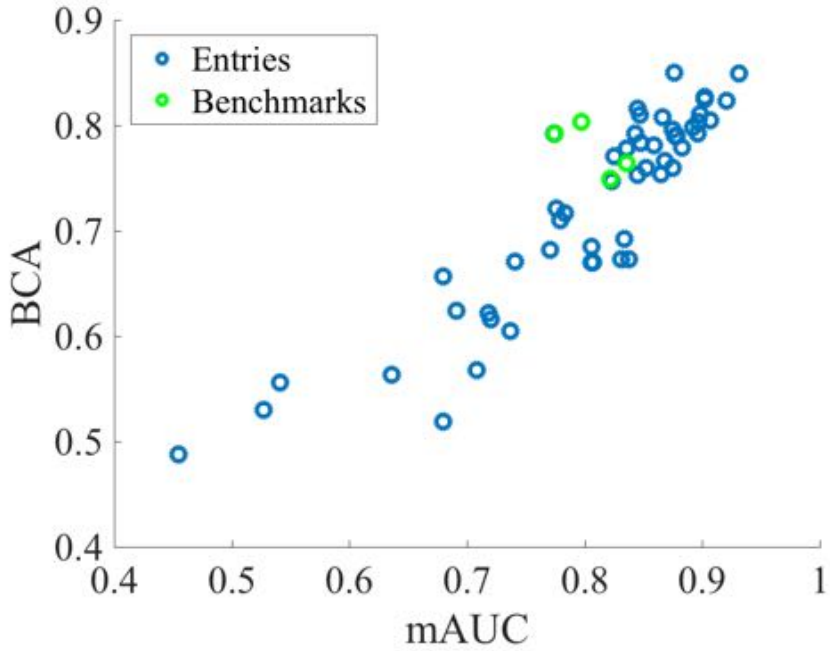


# Evaluation data

| TADPOLE Data set | | D1 | D2 | D3 | D4 |
|---|---|---|---|---|---|
| Number of Subjects | | 1667 | 896 | 896 | 219 |
| Controls | Number (%) | 508 (30.5%) | 369 (41.2%) | 299 (33.4%) | 94 (42.9%) |
| | Visits per subject | 8.3 (4.5) | 8.5 (4.9) | 1.0 (0.0) | 1.0 (0.2) |
| | Age (baseline) | 74.3 (5.8) | 73.6 (5.7) | 72.3 (6.2) | 78.4 (7.0) |
| | Gender (% male) | 48.62% | 47.15% | 43.48% | 47.90% |
| | MMSE (baseline) | 29.1 (1.1) | 29.0 (1.2) | 28.9 (1.4) | 29.1 (1.1) |
| | Converters** | 17 (3.35%) | 8 (2.17%) | - | - |
| MCI | Number (%) | 841 (50.4%) | 458 (51.1%) | 269 (30.0%) | 90 (41.1%) |
| | Visits per subject | 8.2 (3.7) | 9.1 (3.6) | 1.0 (0.0) | 1.1 (0.3) |
| | Age (baseline) | 73.0 (7.5) | 71.6 (7.2) | 71.9 (7.1) | 79.4 (7.0) |
| | Gender (% male) | 59.33% | 56.33% | 57.99% | 64.40% |
| | MMSE (baseline) | 27.6 (1.8) | 28.0 (1.7) | 27.6 (2.2) | 28.1 (2.1) |
| | Converters** | 111 (13.20%) | 34 (7.42%) | - | 9 (10.0%) |
| AD | Number (%) | 318 (19.1%) | 69 (7.7%) | 136 (15.2%) | 29 (13.2%) |
| | Visits per subject | 4.9 (1.6) | 5.2 (2.6) | 1.0 (0.0) | 1.1 (0.3) |
| | Age (baseline) | 74.8 (7.7) | 75.1 (8.4) | 72.8 (7.1) | 82.2 (7.6) |
| | Gender (% male) | 55.35% | 68.12% | 55.88% | 51.70% |
| | MMSE (baseline) | 23.3 (2.0) | 23.1 (2.0) | 20.5 (5.9) | 19.4 (7.2) |
| | Converters** | - | - | - | 9 (31.0%) |

# Results: clinical status

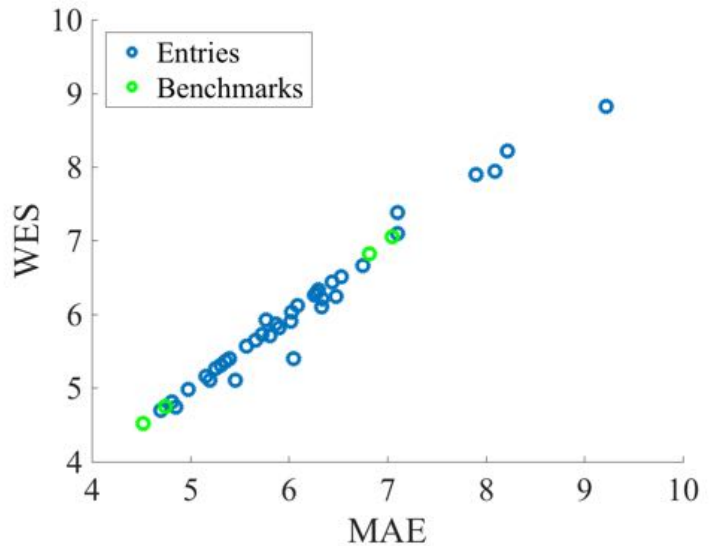
| Team Name | RANK MAUC | MAUC | BCA |
|---|---|---|---|
| | 1 | 0.931 | 0.849 |
| | 2 | 0.921 | 0.823 |
| | 3 | 0.907 | 0.805 |
| | 4-6 | 0.902 | 0.825 |
| | 4-6 | 0.902 | 0.825 |
| | 4-6 | 0.902 | 0.825 |
| | 7 | 0.902 | 0.827 |
| | 8 | 0.898 | 0.811 |
| | 9 | 0.897 | 0.803 |
| | 34 | 0.823 | 0.747 |

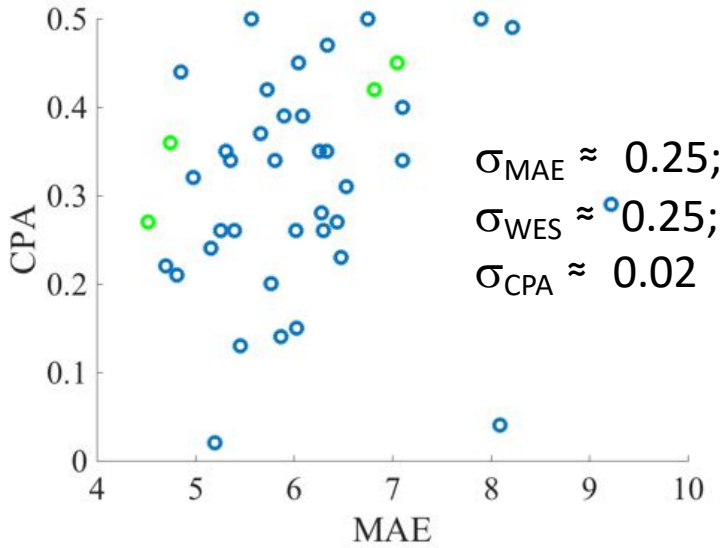



$\sigma_{mAUC} \approx 0.016$; $\sigma_{BCA} \approx 0.025$

# Results: ADAS-COG13

| Team Name | RANK ADAS | ADAS MAE | ADAS WES | ADAS CPA |
|---|---|---|---|---|

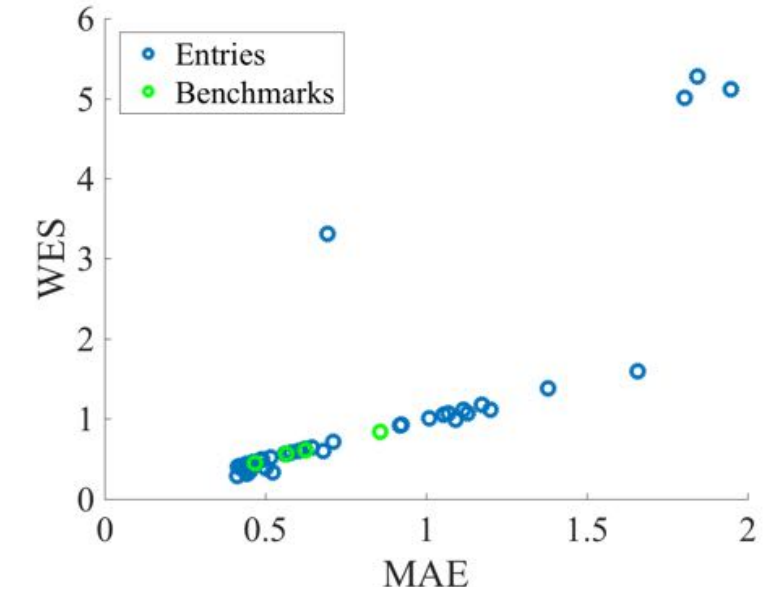


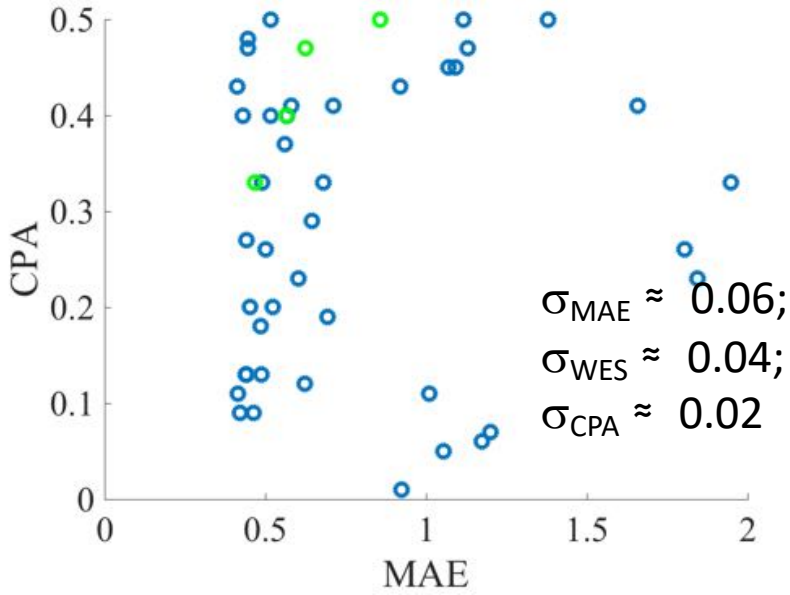




$\sigma_{MAE} \approx 0.25$;
$\sigma_{WES} \approx 0.25$;
$\sigma_{CPA} \approx 0.02$

# Results: ventricle volume

| Team Name | RANK VENTS | VENTS MAE | VENTS WES | VENTS CPA |
|---|---|---|---|---|
| | | 0.4116 | 0.2857 | 0.43 |
| | | 0.4116 | 0.2857 | 0.43 |
| | | 0.4155 | 0.4072 | 0.11 |
| | | 0.4207 | 0.4108 | 0.09 |
| | | 0.4299 | 0.3739 | 0.4 |
| | | 0.4402 | 0.4209 | 0.13 |
| | | 0.4409 | 0.4409 | 0.27 |
| | | 0.441 | 0.3109 | 0.13 |
| | | 0.4466 | 0.403 | 0.48 |
| | | 0.4469 | 0.3274 | 0.47 |
| | | 0.4534 | 0.354 | 0.2 |
| | | 0.4534 | 0.354 | 0.2 |
| | | 0.4625 | 0.4625 | 0.09 |
| RandomisedBest | 14 | 0.467 | 0.4492 | 0.33 |




$\sigma_{MAE} \approx 0.06$;
$\sigma_{WES} \approx 0.04$;
$\sigma_{CPA} \approx 0.02$

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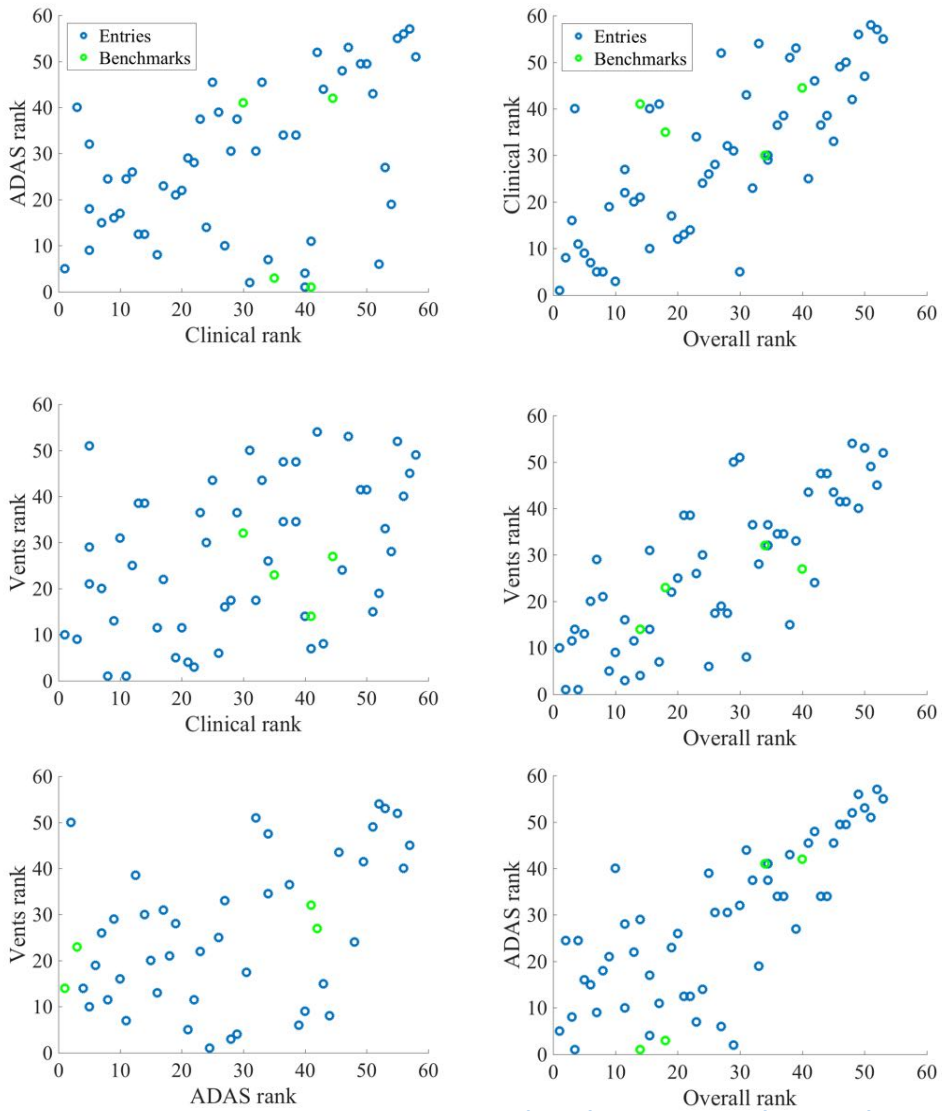
# Results: overall winners

| Team Name | RANK | RANK MAUC | RANK ADAS | RANK VENTS |
|---|---|---|---|---|



# Results: D3 overall ranking

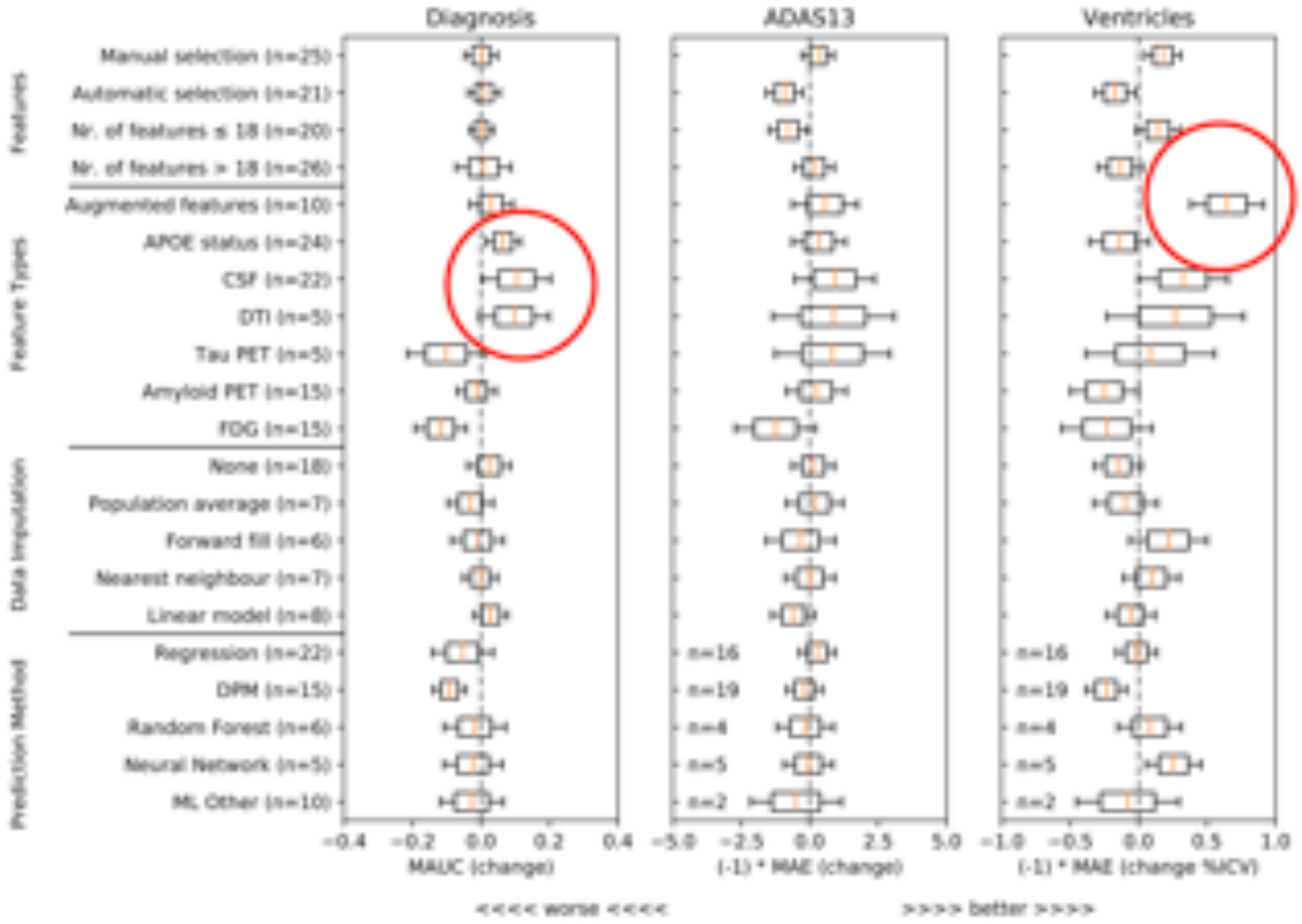
| Team Name | RANK | RANK MAUC | RANK ADAS | RANK VENTS |
|---|---|---|---|---|

# Prize summary

| Category | Team | Members | Institution | Country | Prize |
|---|---|---|---|---|---|
| Overall best | Frog | Keli Liu, Paul Manser, Christina Rabe | Genentech | USA | £5,000 |

# Lessons in AD prediction

- DTI and CSF features for clinical diagnosis prediction
- Augmented features for ventricle prediction
- However, further analysis needs to be done to make clear conclusions




Slide credit: Raz Marinescu
http://www.mit.edu/~razvan/

# Lessons in AD prediction: summary


- **Clinical Diagnosis**: best algorithms achieve considerable gains over benchmarks
  - Gradient boosting
- **Ventricle volume**: same (but different algorithm!)
  - Disease progression modelling
- **ADAS-Cog13**: FAIL.
  - Random guessing did better (best of 100 guesses)

- No single algorithm wins all
- Deep learning doesn't win (best: 5$^{th}$ place)
- **Consensus methods** outperform all. (Most systematic errors: over/under-predict)

https://arxiv.org/abs/2002.03419

# Acknowledgements



- Sponsors





- Participants

- Organisers and advisors:
  - Raz Marinescu and Neil Oxtoby
  - Esther Bron, Stefan Klein, Alex Young, Sara Garbarino
  - Frederik Barkhof, Nick Fox
  - LONI team at USC, The ADNI Consortium.