Optimizing the use of CSF AD biomarkers: unbiased and precise cut-offs

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IDDI
ADDING VALUE TO CLINICAL DATA

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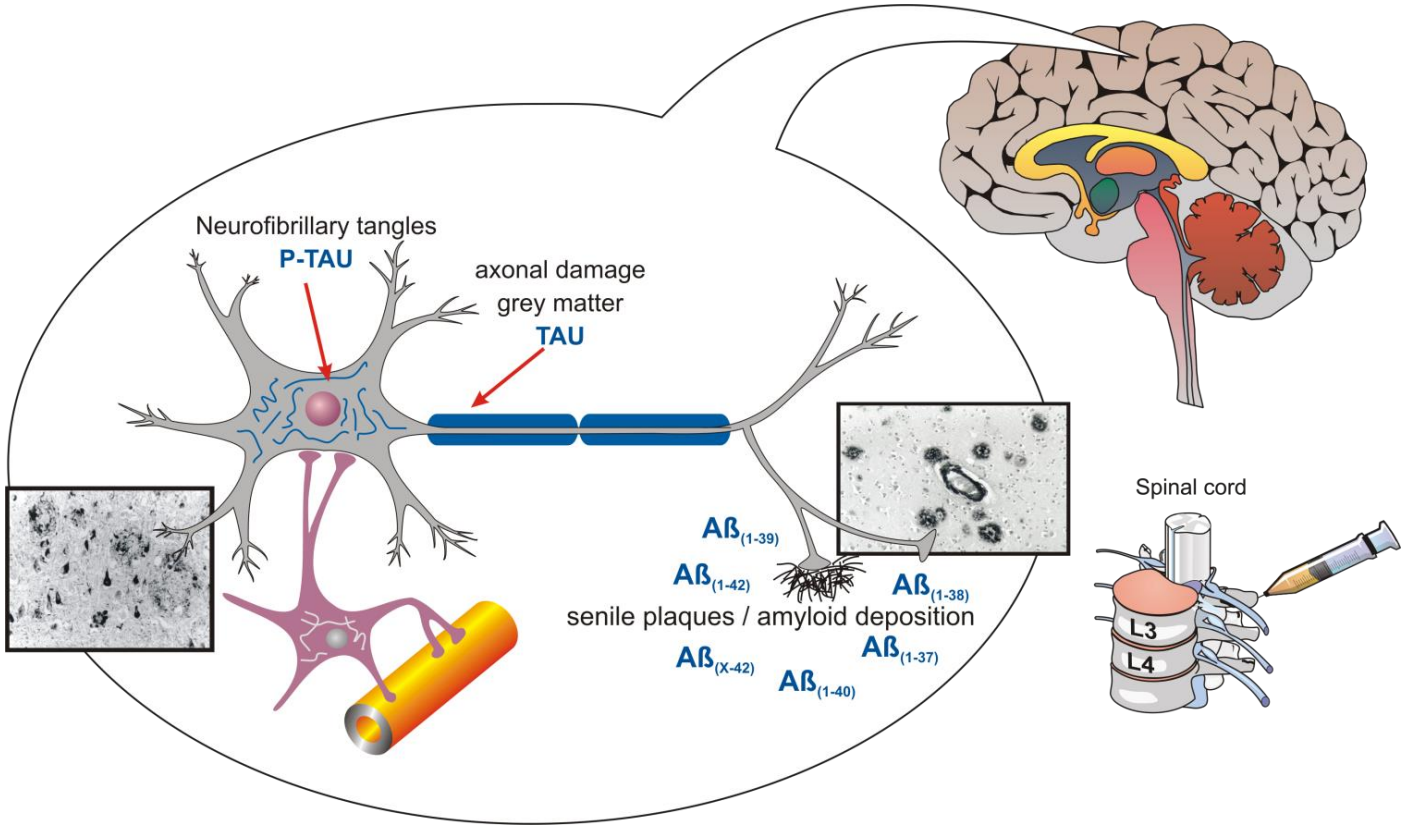
Content

I. Introduction: biomarkers and cut-offs
II. Bias in the cut-off estimate
  – Not correcting for an imperfect reference test
  – Transfer of a cut-off between assays/labs
III. Imprecision of the cut-off estimate
IV. Reporting and applying cut-offs
V. Conclusion

I. INTRODUCTION

CSF AD biomarkers

- Cerebrospinal fluid biomarkers (CSF) linked with hallmarks of disease



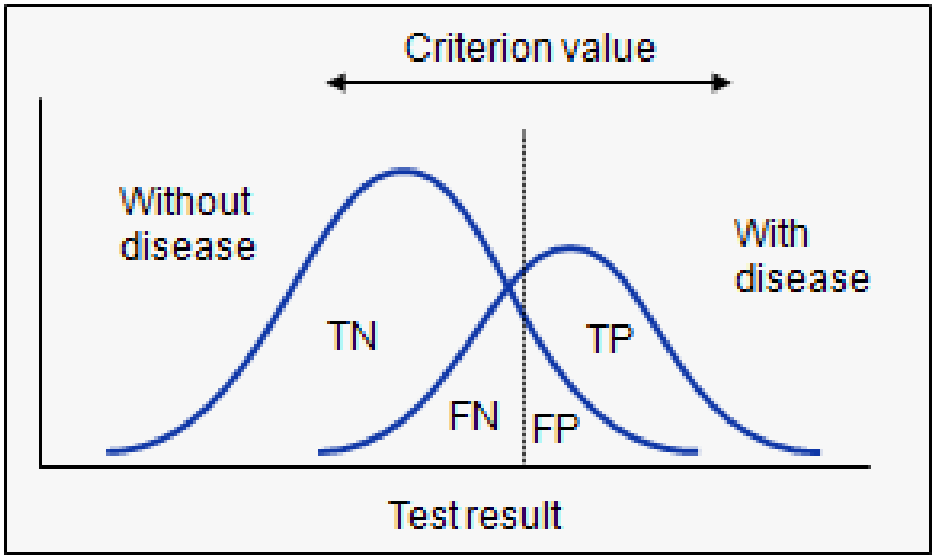
Vanderstichele et al, 2008

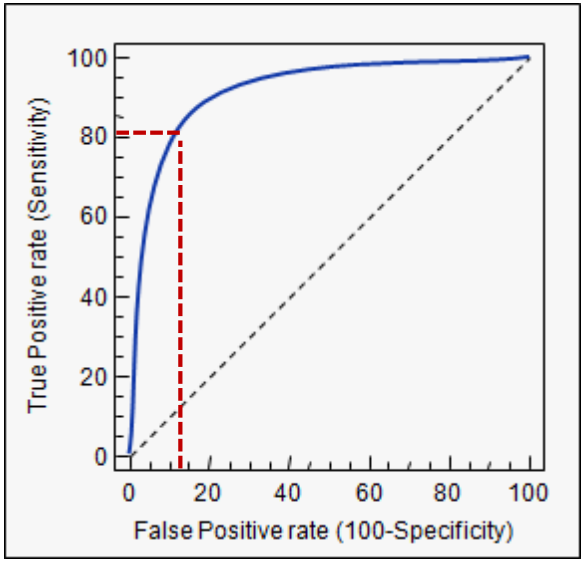
CSF AD biomarkers

- Continuous measurements
  - Dichotomized for clinical use
  - Decision threshold (= cut-off)
- Biomarker levels of 'healthy' and 'diseased' populations overlap
  - No perfect diagnostic performance (100% sensitivity + 100% specificity)
  - 'Optimal' cut-off selected
  - 'Optimal' is biomarker- and intended use-specific

Cut-off selection

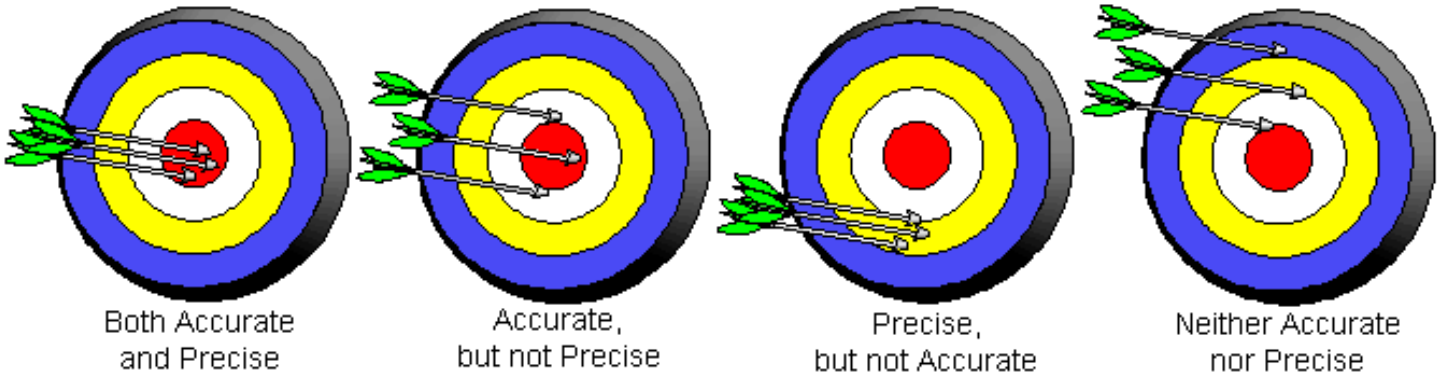
- Requires
  1. Reference test results indicating the subjects' true disease status
  2. Biomarker levels for healthy and diseased subjects
- Commonly performed by construction of a ROC-curve + selection of the 'optimal' cut-off





Cut-off selection

- Selected cut-off is only an estimate of the true optimal cut-off
  - Estimated cut-off should be unbiased (accurate) and precise
  - Both bias and imprecision can result in sub-optimal cut-offs



Cut-off properties

- Precision is linked to sample size, bias not
- If an estimate is biased, including more samples of the same population and using the same analysis, will increase precision of the estimate but will not remove the bias!

Using an imperfect reference test

II. BIAS IN THE CUT-OFF ESTIMATE

Clinical diagnosis is an imperfect reference test for AD pathology

- Consider
  - Clinical diagnosis not always correct
  - Biomarker does not tend to misclassify same subjects as clinical diagnosis
- Biomarker forced to recover possibly flawed clinical diagnosis
  - Biomarker penalized for correctly assigning misdiagnosed subjects
  - Diagnostic performance biomarker underestimated
  - ➢ Biased ROC-curve and cut-off

Clinical diagnosis is an imperfect reference test for AD pathology

- Toledo et al. 2012, differential diagnosis setting
  - Different cut-offs obtained when clinical and neuropathological diagnosis used as reference test (and considering the reference test to be perfect)
- Coart et al. JAD 2015
  - 'Classical' analysis results in biased ROC & cut-off
  - ➢ New Bayesian methodology that accounts for error in the reference test

Transferring a cut-off with an inappropriate method

II. BIAS IN THE CUT-OFF ESTIMATE

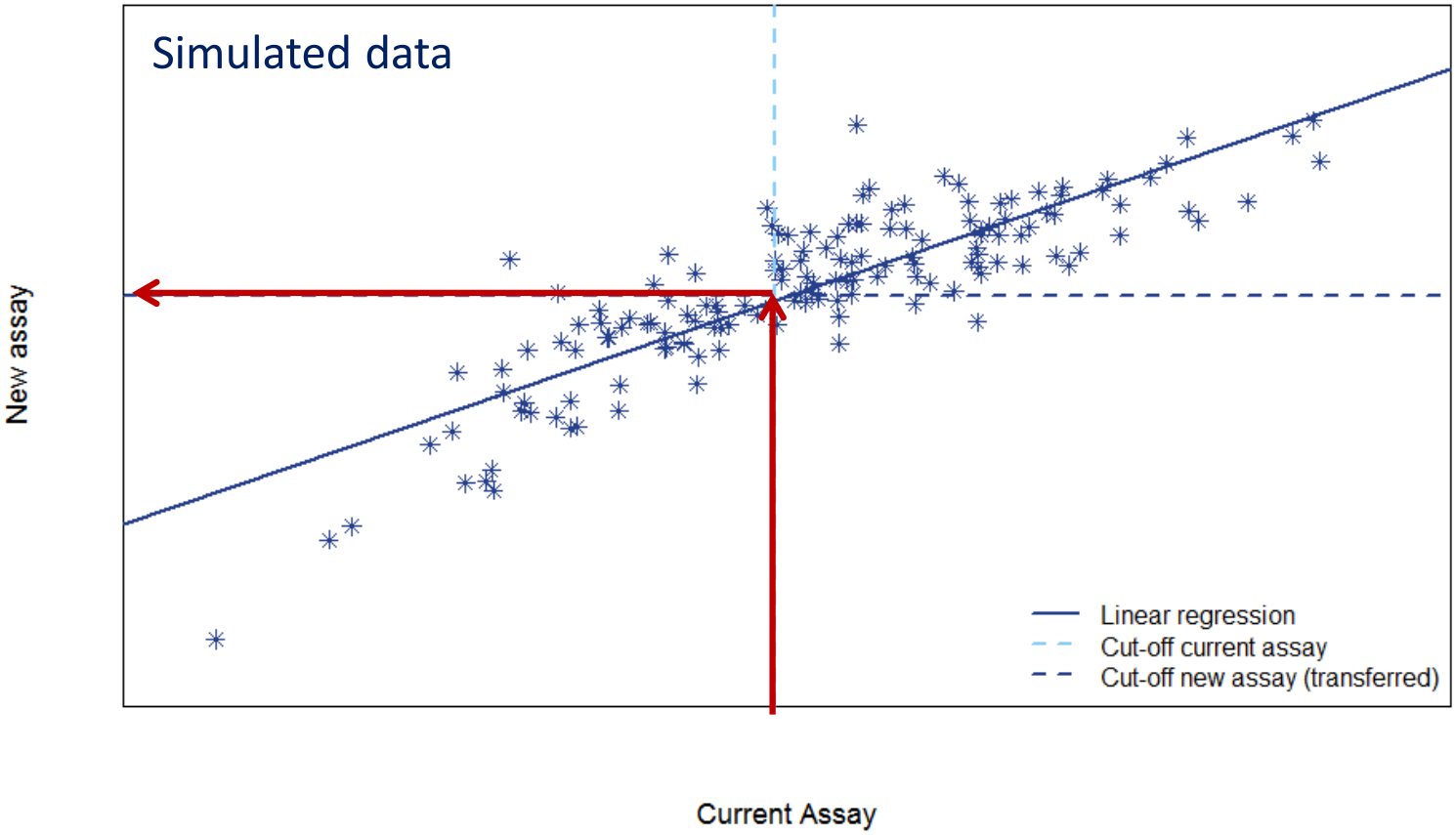
Cut-off transfer

- Different assays measuring the 'same' analyte report different concentrations
- Different labs measuring the same analyte with the same assay report different concentrations

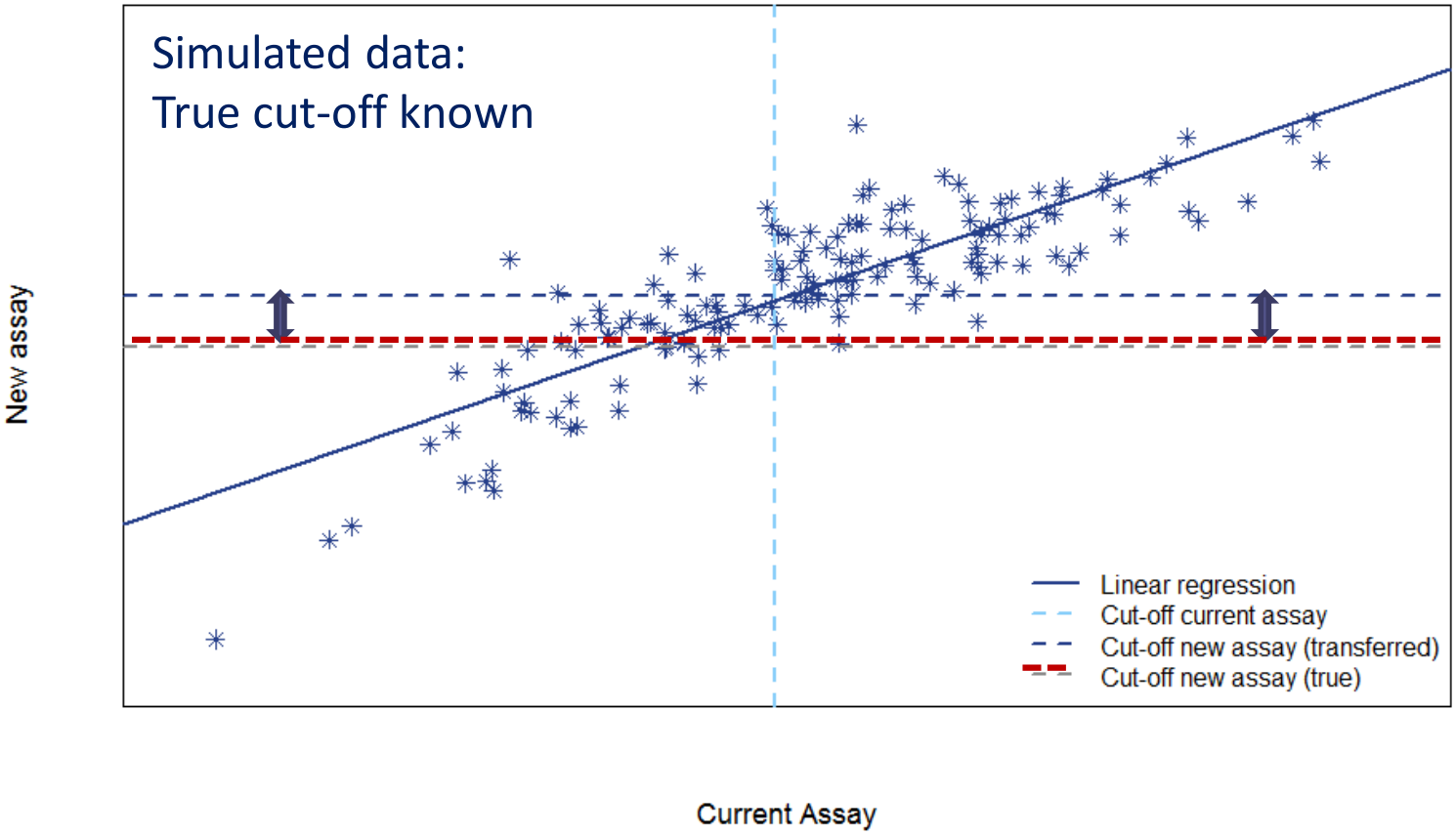
➢ Need for assay- and lab-specific cut-off

- In absence of well-characterized samples, cut-off is transferred from current assay to new assay
- 'Side-by-side' testing of samples and cut-off transferred with linear regression

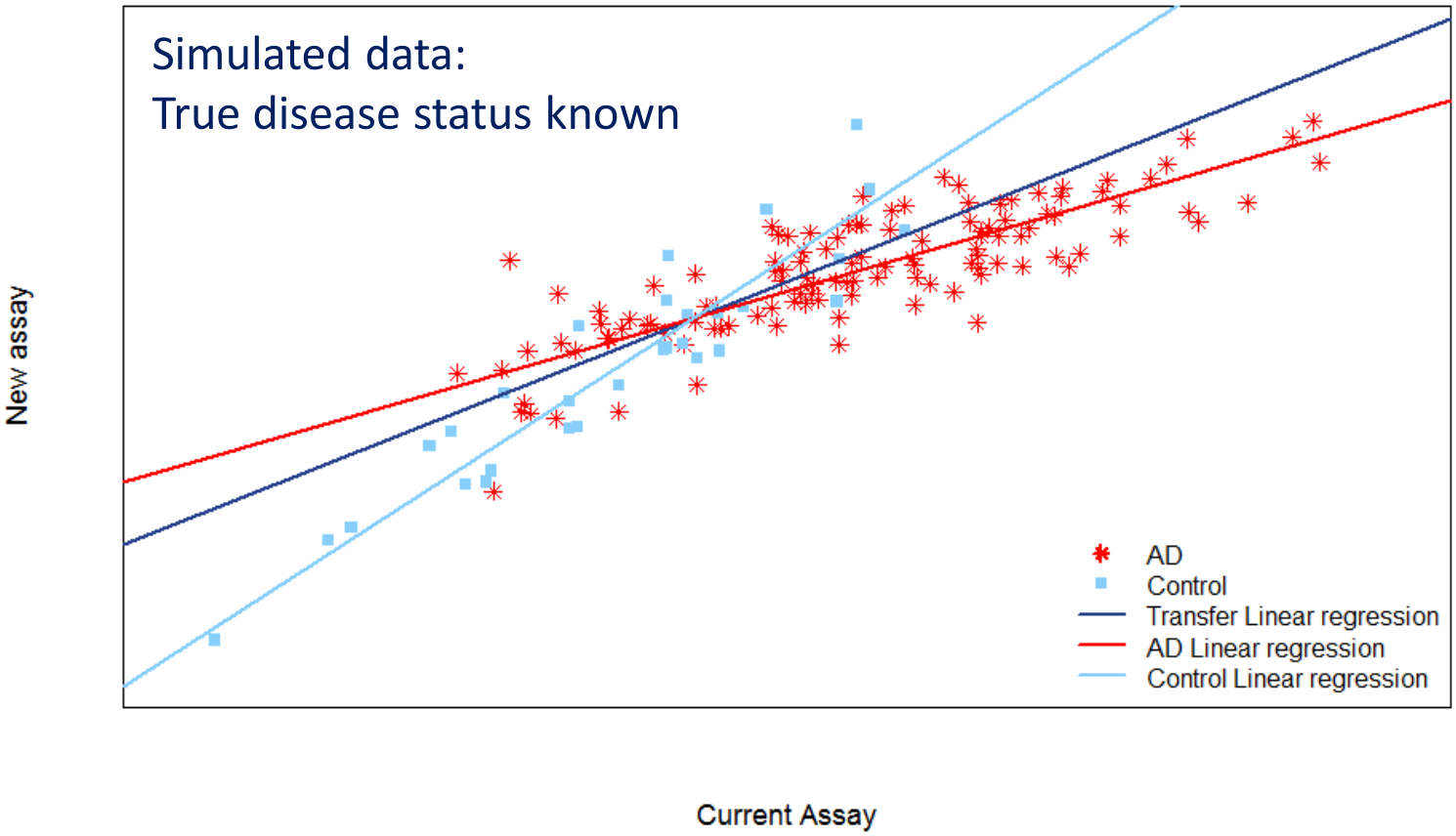
Cut-off transfer
General methodology: linear regression



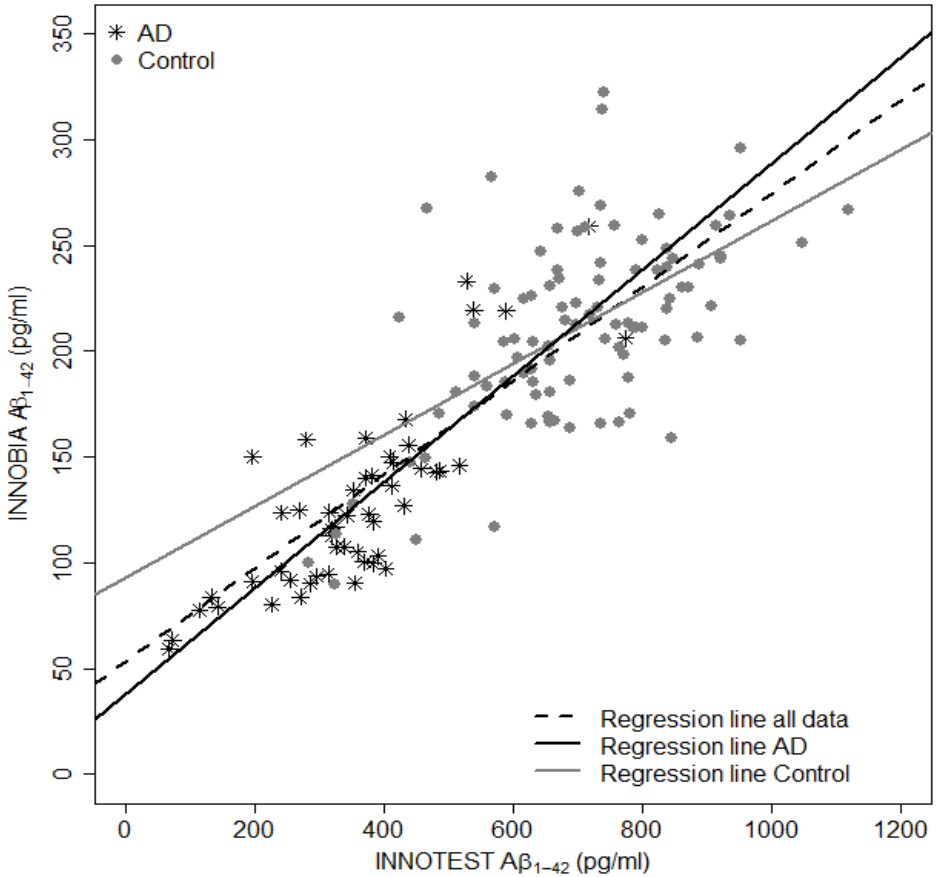
Cut-off transfer
Bias in transferred cut-off



Cut-off transfer
Where does the bias come from?



Realistic that linear regression is different between groups?



- Dataset BIODEM lab, Antwerp University (Le Bastard et al. JAD 2013)
- AD = pathologically confirmed AD
- $A\beta_{1\text{-}42}$ concentration measured in same samples with 2 assays

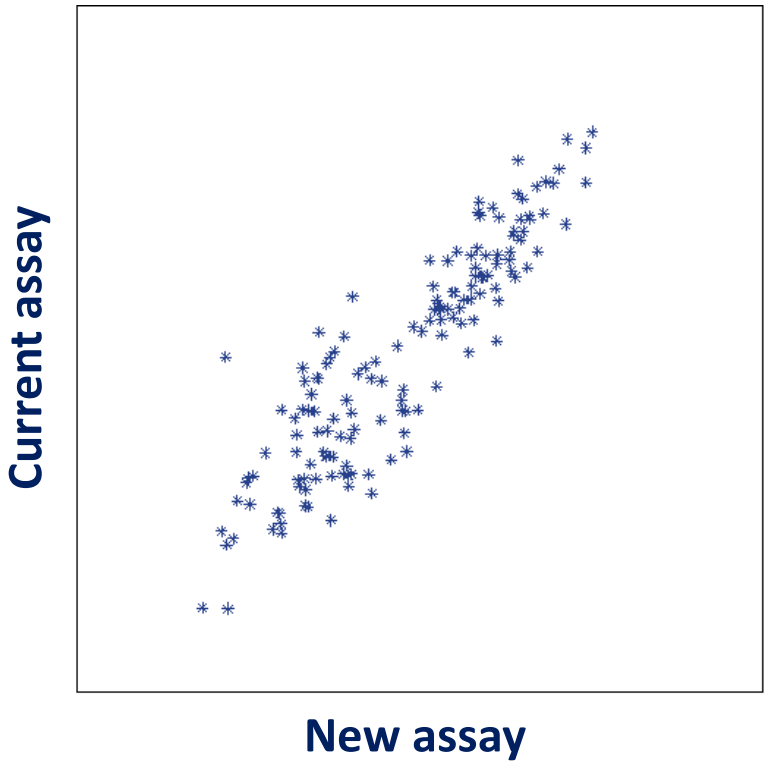
➢ Different relationship between assays in AD and control population

García Barrado et al., submitted

Cut-off transfer: New methodology

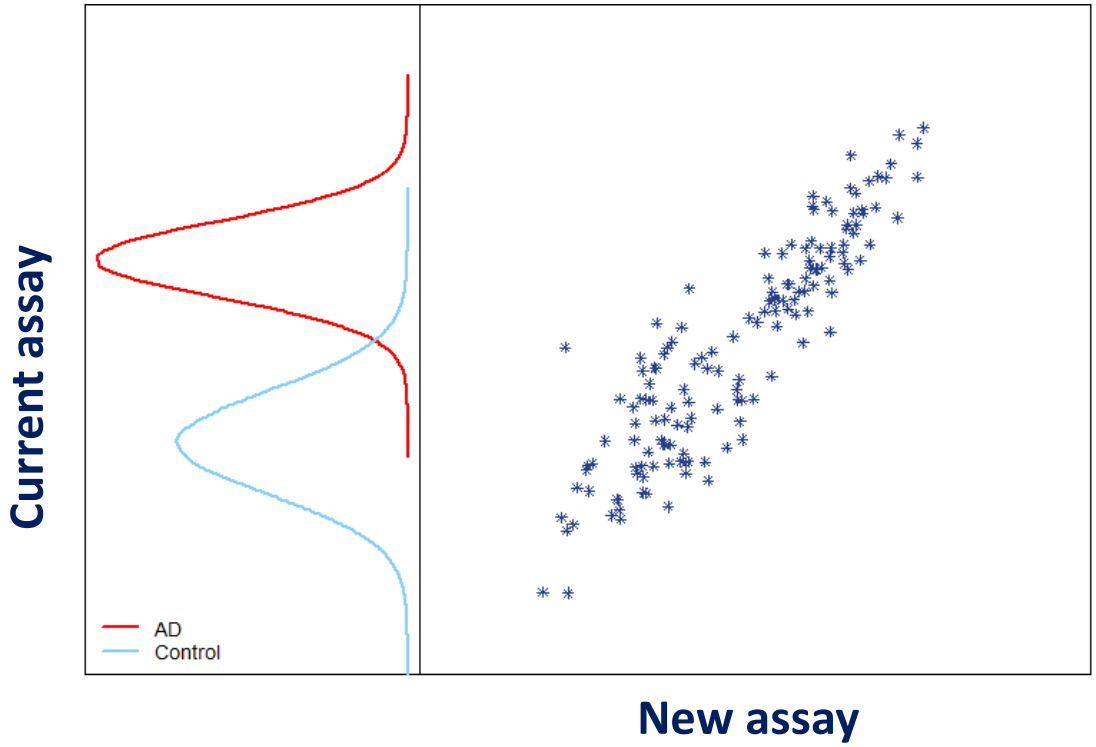
- Bayesian 2-stage method, using original cut-off study as prior information for cut-off transfer
- Results in unbiased and less variable cut-off estimates
- García Barrado, Coart, Vanderstichele, Burzykowski, submitted to Clinical Chemistry

Cut-off transfer: Bayesian 2-stage method



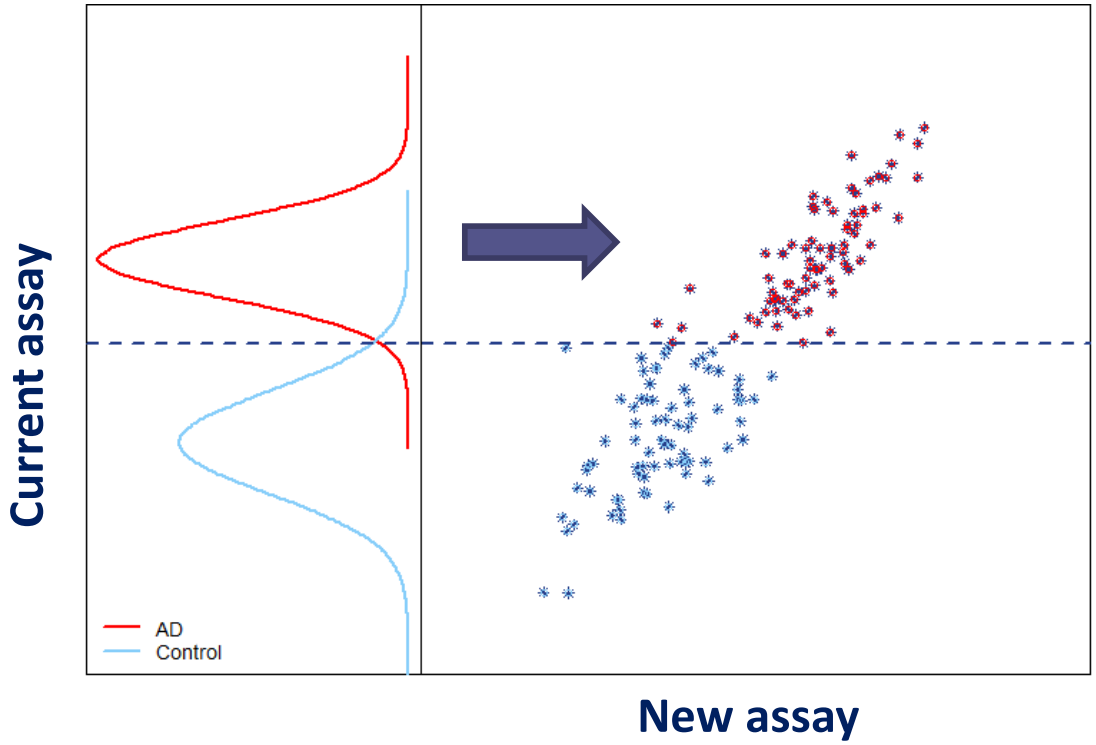
- ‘Transfer’ dataset: no information on disease status

Cut-off transfer: Bayesian 2-stage method



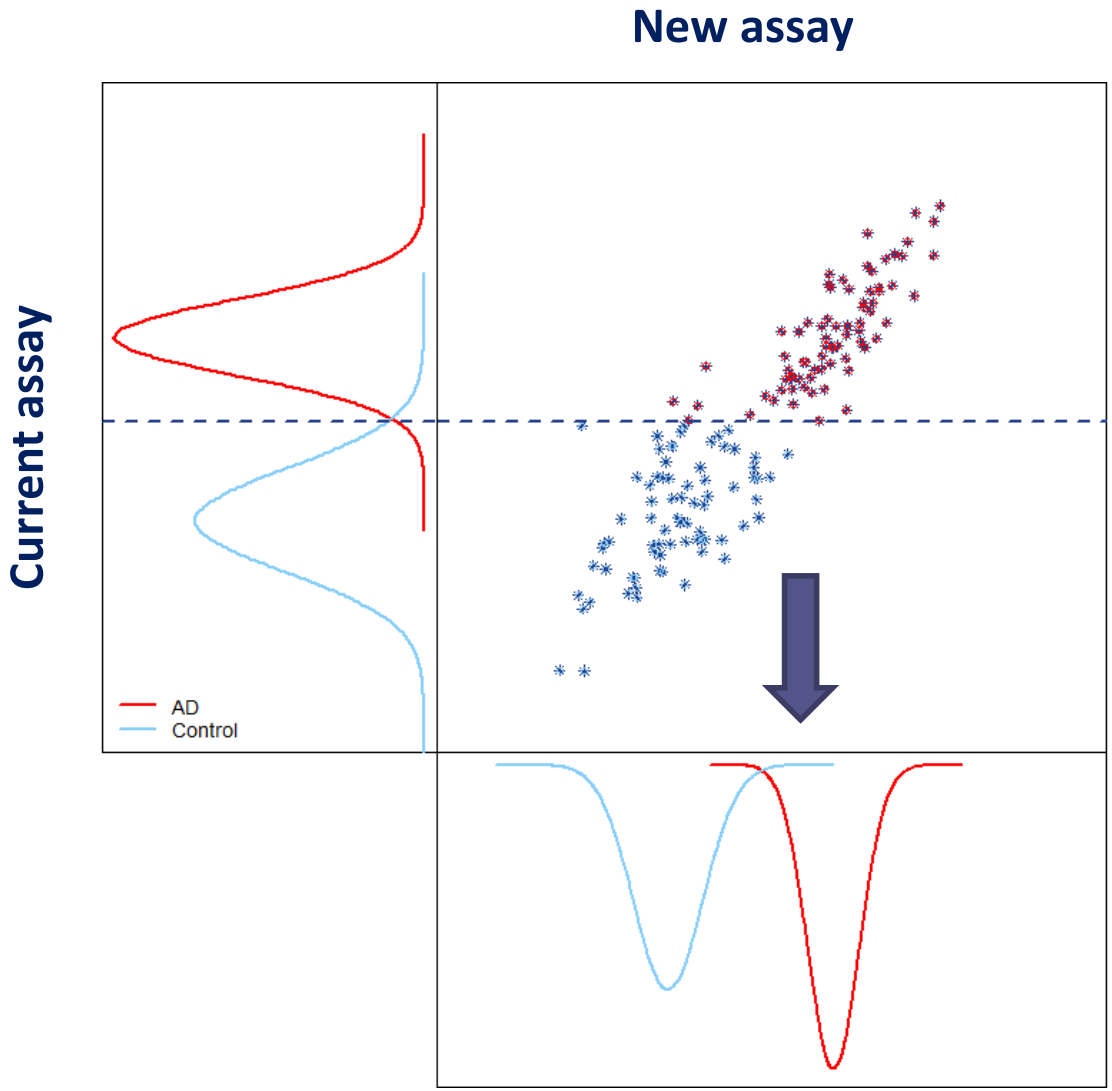
- 'Transfer' dataset: no information on disease status
- But original cut-off setting dataset contains disease status → use as prior information

Cut-off transfer: Bayesian 2-stage method



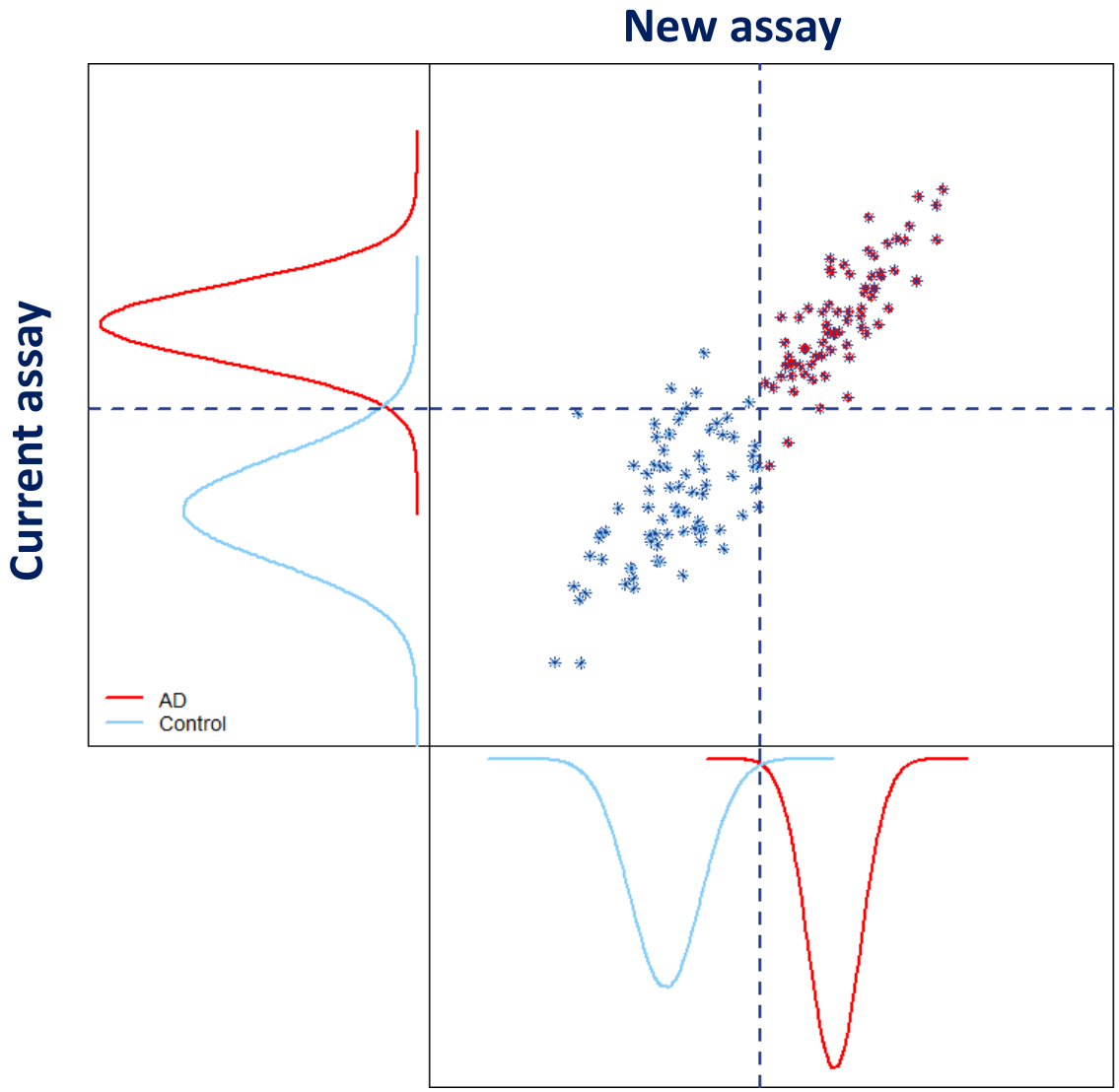
- Predict disease status of subjects in ‘transfer’ dataset

Cut-off transfer: Bayesian 2-stage method



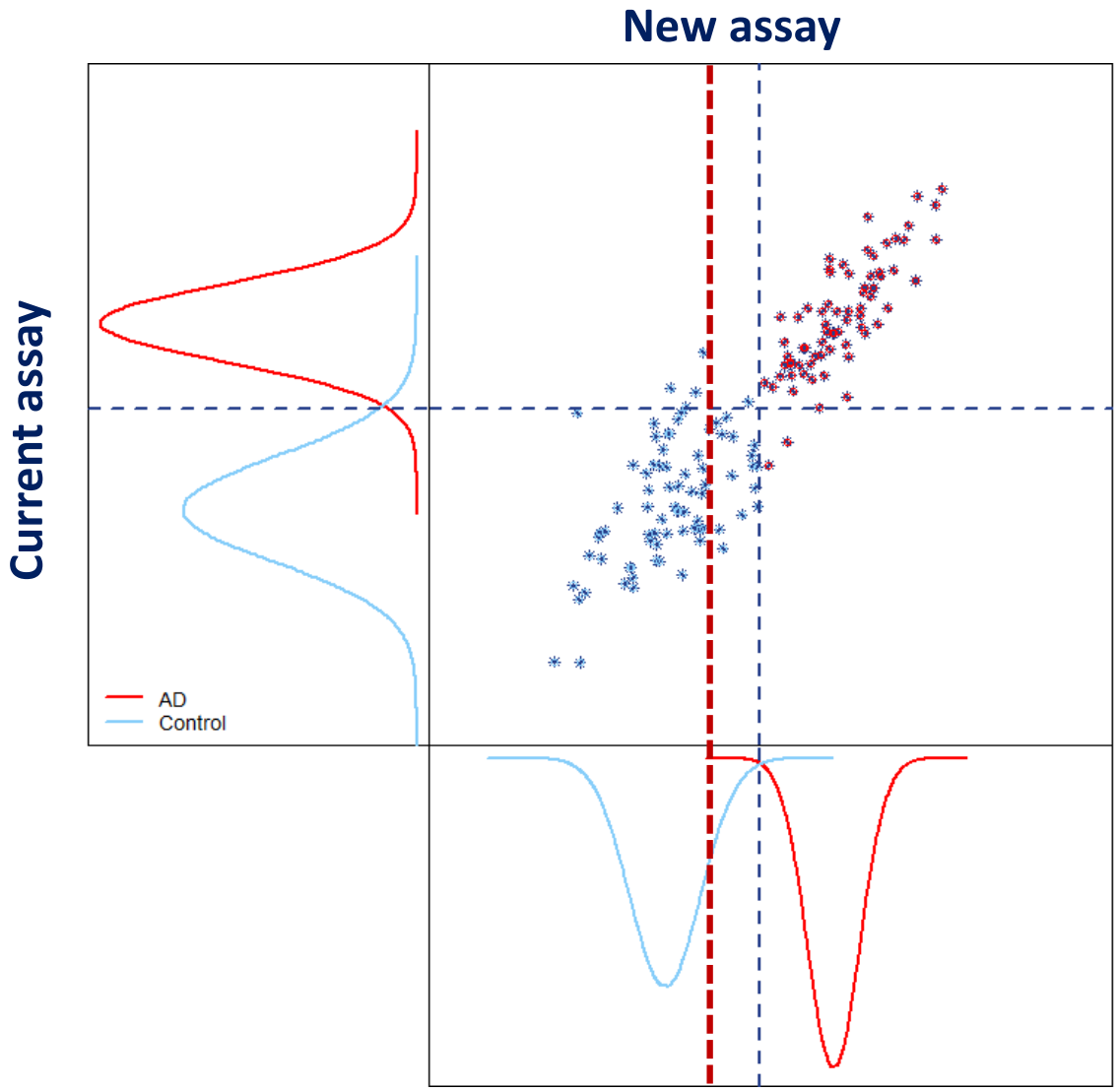
- Estimate distributions of biomarker measured with new platform with predicted disease status

Cut-off transfer: Bayesian 2-stage method



- Derive cut-off for new assay

Cut-off transfer: Bayesian 2-stage method



- Derive cut-off for new assay
- Compare with linear regression cut-off

III. IMPRECISION OF THE CUT-OFF ESTIMATE

Italian dataset

Journal of Alzheimer's Disease 29 (2012) 229–238
DOI 10.3233/JAD-2011-111349
IOS Press

Performance of $A\beta_{1-40}$, $A\beta_{1-42}$, Total Tau, and Phosphorylated Tau as Predictors of Dementia in a Cohort of Patients with Mild Cognitive Impairment

Lucilla Parnetti[a,*,1], Davide Chiasserini[a,d,1], Paolo Eusebi[b], David Giannandrea[a], Gianni Bellomo[c], Claudia De Carlo[a], Chiara Padiglioni[a], Sara Mastrocola[a], Viviana Lisetti[a,d] and Paolo Calabresi[a,d]
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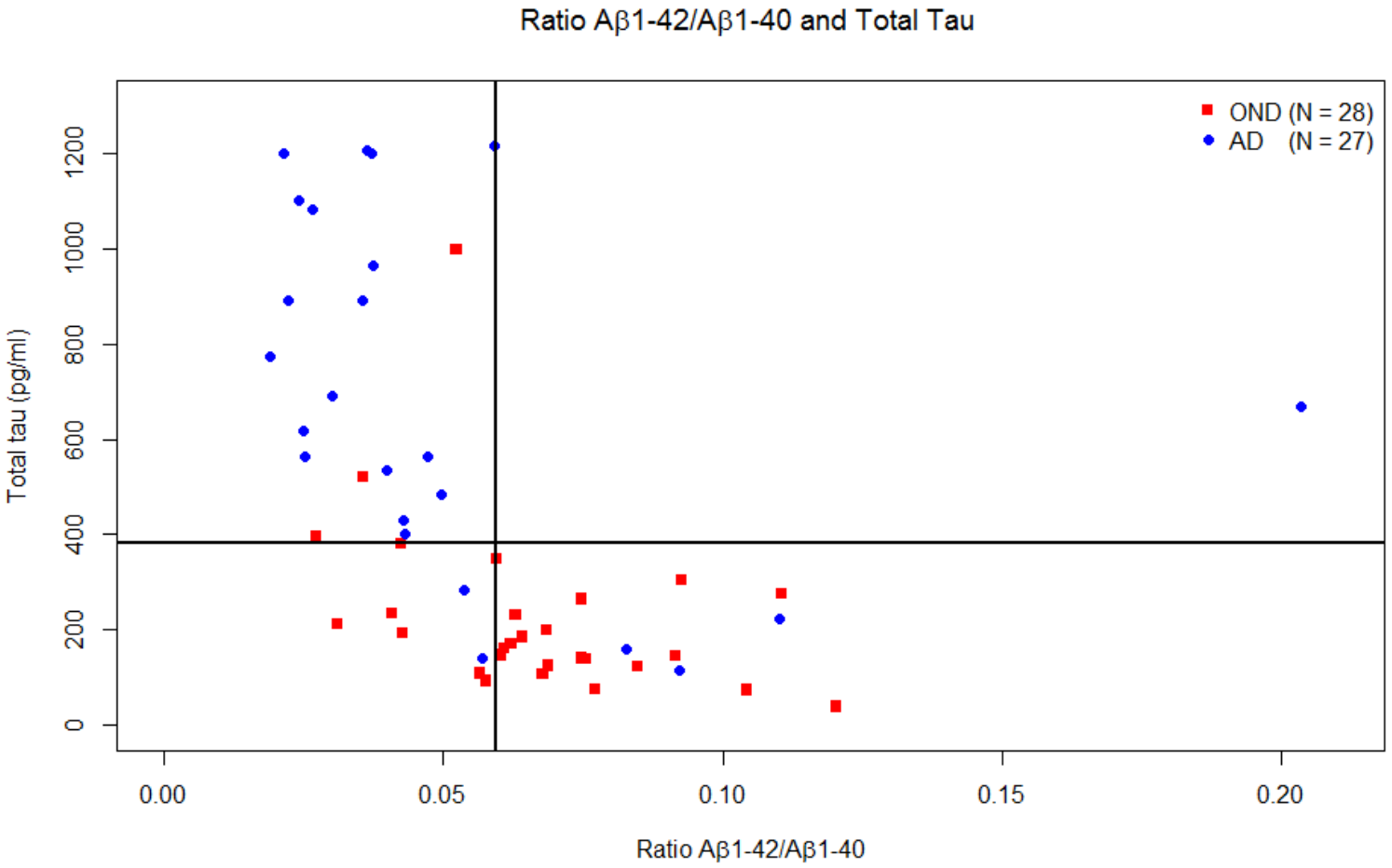
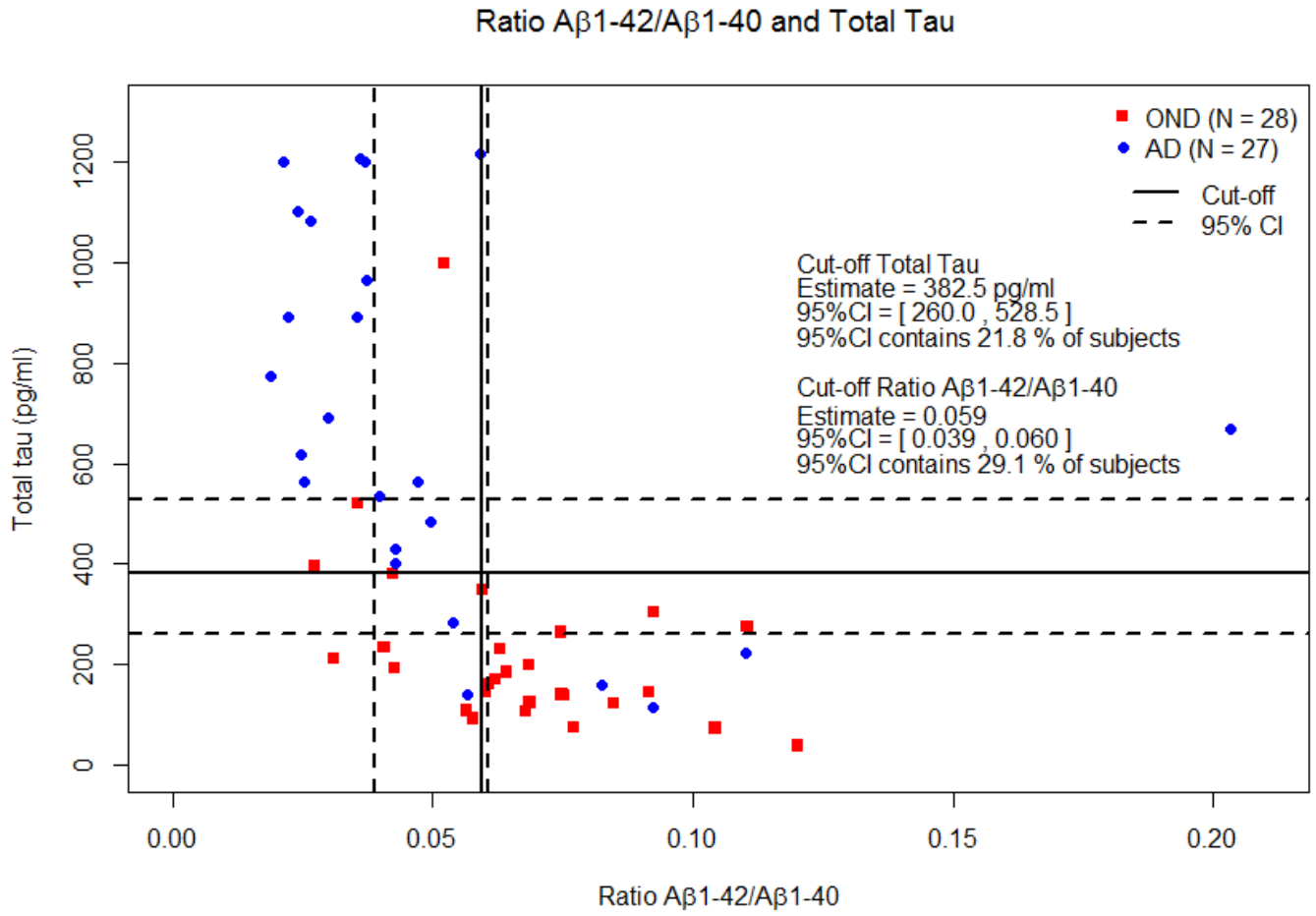
[c]*Ospedale S.Giovanni Battista, Foligno, Italy*
[d]*Fondazione S. Lucia, I.R.C.C.S. Rome, Italy*

- Cut-off ratio $A\beta_{1-42}/A\beta_{1-40}$ and Total tau for discrimination AD vs. OND

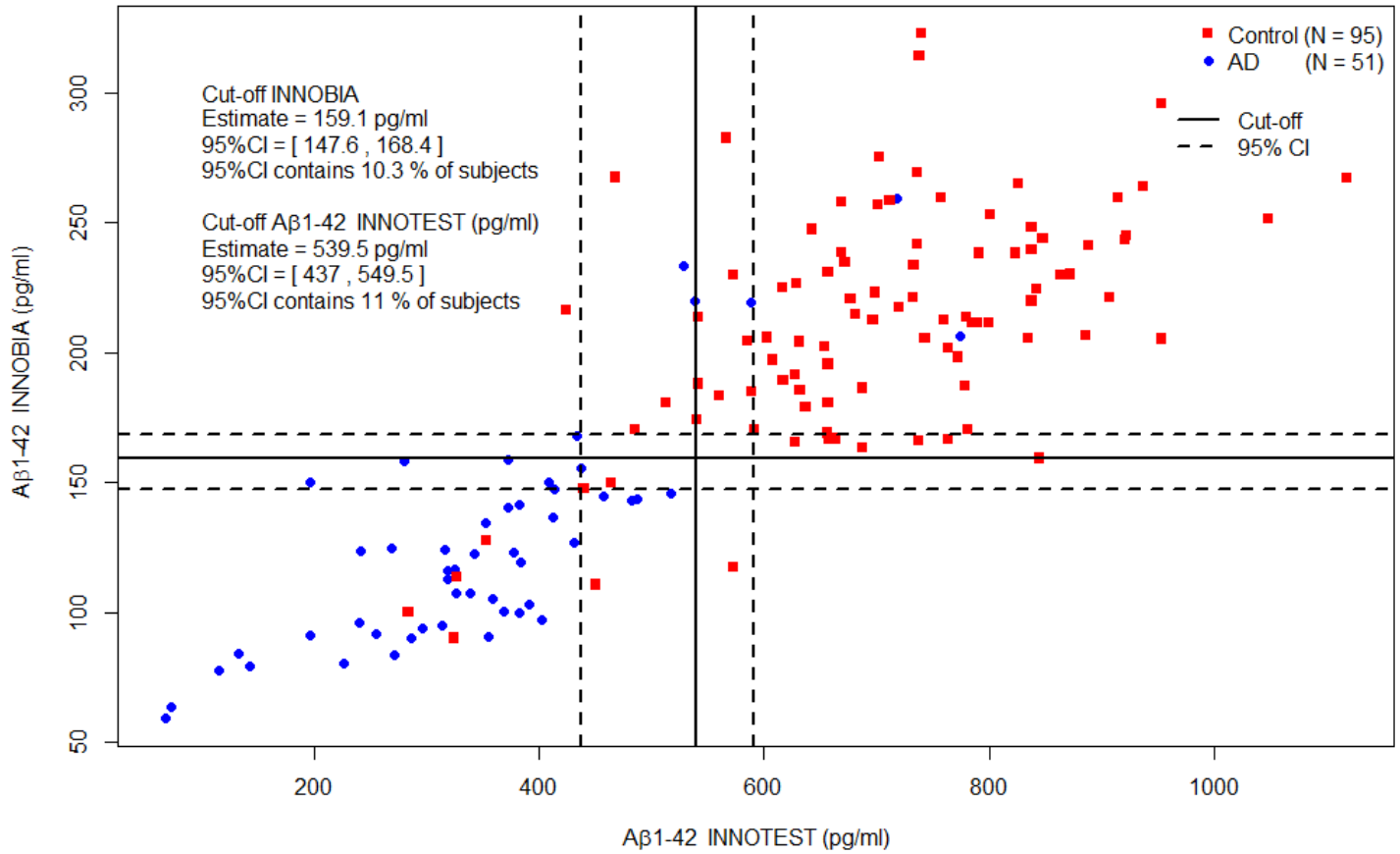
Estimating optimal cut-offs



Imprecision of cut-off estimates



Imprecision of cut-off estimates BIODEM dataset*



* Le Bastard et al. JAD 2013

Acceptance criteria for cut-off precision ‘How precise is precise enough?’

Expressed as function of the cut-off’s 95% CI

- Width not exceeding a certain proportion of the clinical range
- Maximal proportion of subjects with biomarker values contained within the 95% CI on the cut-off estimate
  - Closer link with intended use

IV. REPORTING AND APPLYING CUT-OFFS

Current practice

- Often statistical methodology not reported
- Often cut-off estimated on limited data
- Imprecision is not reported
- Imprecision ignored in clinical practice

➢ The estimated cut-off is treated as the true optimal cut-off

Suggestions for improvement

- Report applied methodology
- Report cut-off + 95% CI
- Treat the 95% CI as ‘grey zone’
  - Values in 95% CI are considered “inconclusive”
- Update cut-off after testing more subjects to increase proportion of conclusive results

➢ More complex but more realistic approach

V. Conclusions

- Established biomarker cut-offs are estimates of the true optimal cut-offs and need to be unbiased and precise
- Estimated cut-offs can be biased
  - Use of imperfect reference test
  - Cut-off transferred with linear regression, …
- Acceptance criteria for precision of cut-off estimate needed

Acknowledgements

- Bas Engelborghs (UA, Biodem)
- Hugo Vanderstichele (ADx NeuroSciences)
- EURO-transbio program

Backup slides

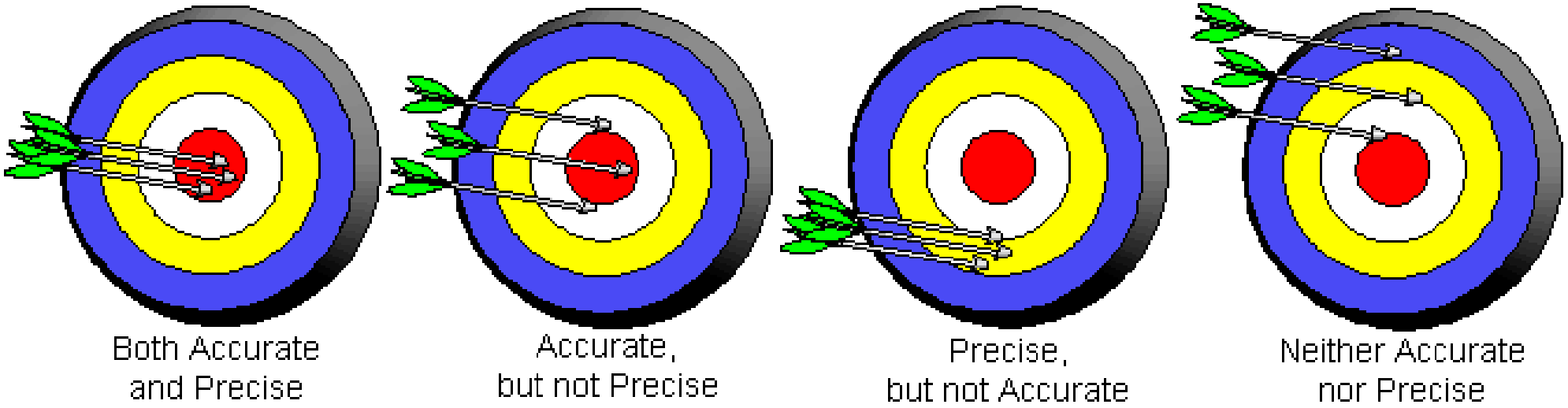
Biomarkers

- A characteristic that is objectively measured and evaluated as an indicator of normal biological processes, pathogenic processes, or pharmacologic responses to a therapeutic intervention*
- Link with pathological process not necessarily known but increases biomarker's credibility

* Biomarkers Definitions Working Group. Biomarkers and surrogate endpoints: preferred definitions and conceptual framework. Clin. Pharmacol. Ther. 69, 89–95 (2001).

Cut-off properties

- Estimated cut-off should be unbiased (accurate) and precise

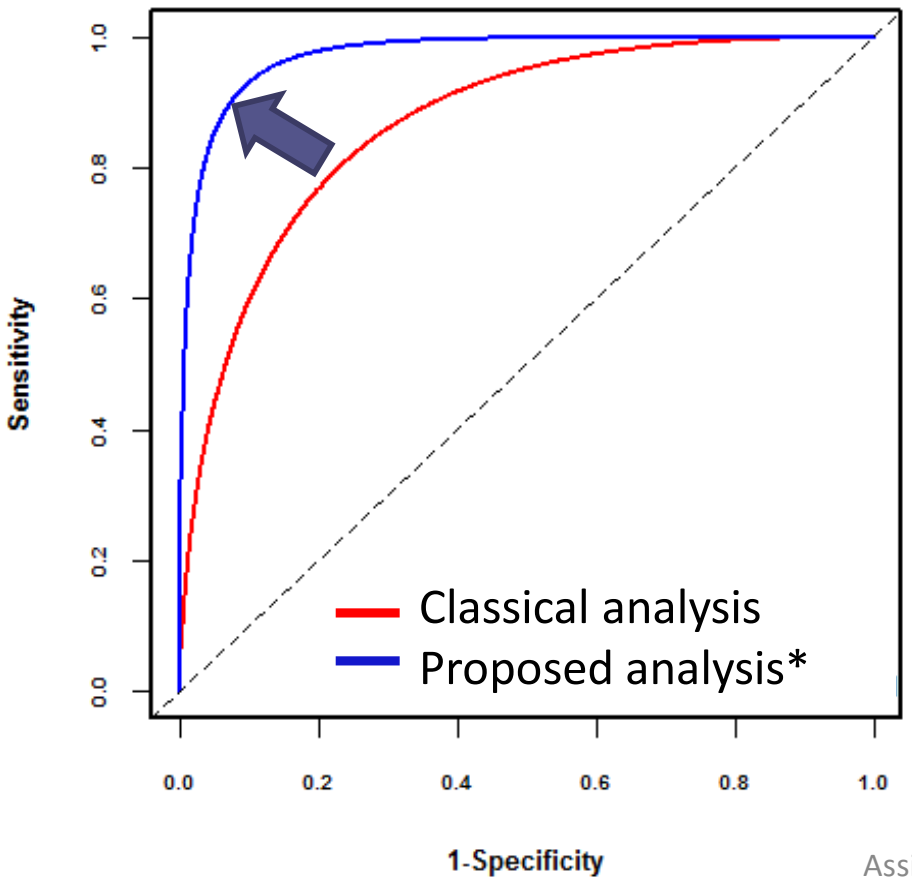


Using an imperfect reference test

- 'Gold Standard' AD diagnosis
  - Neuropathological AD confirmation
  - Not often available
- Current practice
  - Clinical diagnosis used as reference test
  - Imperfectness of clinical diagnosis acknowledged but ignored
  - ➢ Can potentially lead to biased biomarker accuracy estimates and cut-offs

Accounting for the imperfect reference test in the statistical analysis

ADNI-I data, AD vs Control
CSF $A\beta_{1\text{-}42}$, T-tau and P-tau_{181p}



Proposed methodology*:

- Bayesian approach
- Consider clinical diagnosis as a biomarker for AD

➢ Shifts ROC curve upwards

*Coart et al. JAD 2015