Modelling response to antiretroviral therapy without a genotype as a clinical tool for resource-limited settings

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HIV Resistance Response Database Initiative

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hiv resistance response database initiative

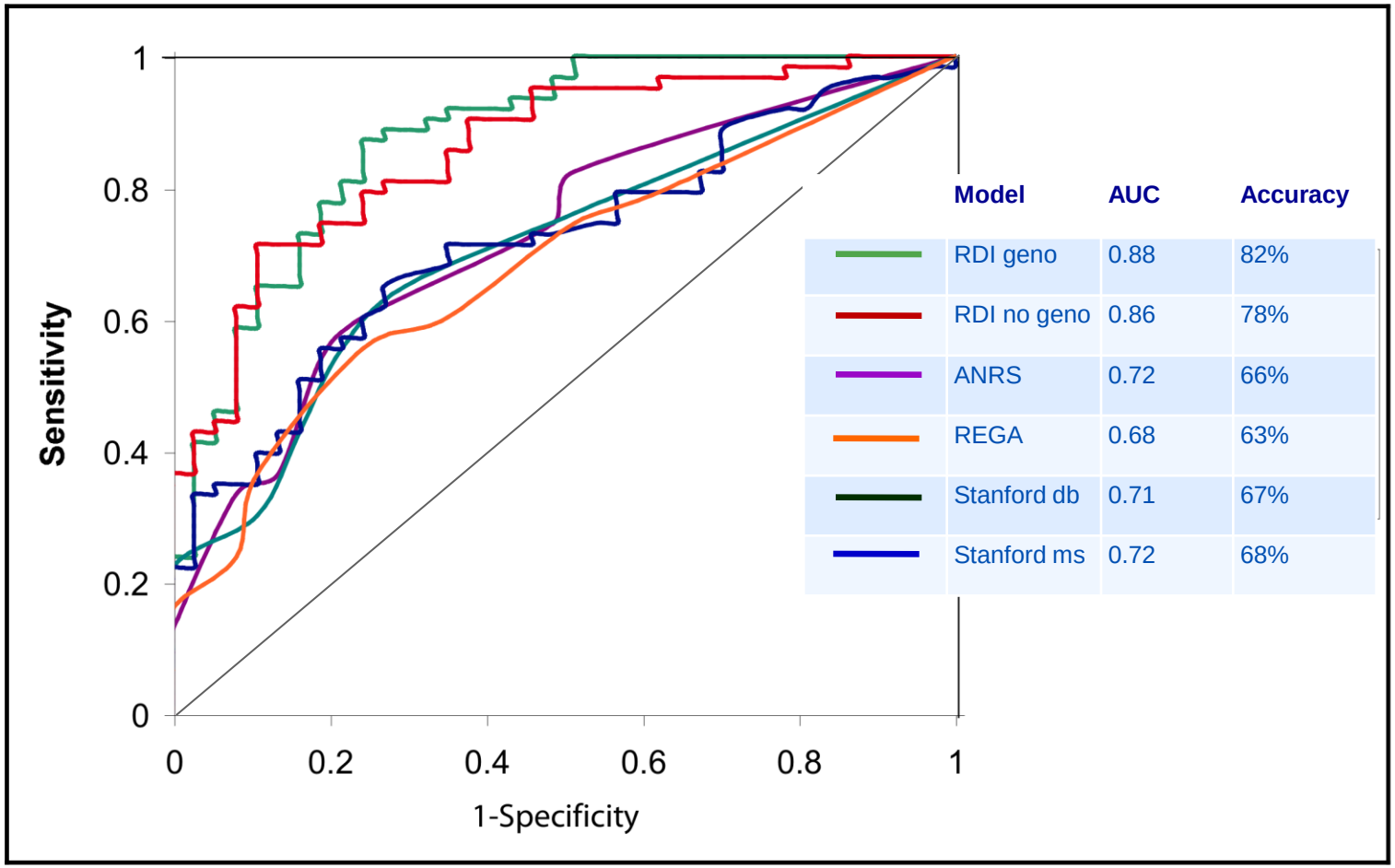
ART in resource-limited settings

- The WHO recently reported that at the end of 2010, 6.6 million people were receiving cART in resource-limited settings
- Treatments are failing at a comparable rate to other settings with resistance a significant factor
- Selecting the optimum drug combination after failure is a major challenge:
  - Resistance testing is not widely available
  - Treatment options are limited
  - Healthcare provider experience may be limited
- Could the RDI's approach be adapted to work without genotypes to help?

The RDI's approach

- RDI global database (75,000 patients) predominantly from 'rich' countries
- Patient response data, including the genotype, are used to train computational models (random forest) to predict probability of virological response
- RF models typically achieve accuracy of ≥ 80% compared with 60-70% for GSS (genotyping + rules)
- Models now available as an aid to treatment selection through the on-line tool 'HIV-TRePS'
- Models trained to predict response without a genotype have relatively small (≤5%) loss of accuracy
- 'No genotype' models trained specifically with data from 'rich' countries resembling 2nd line treatment in RLS were 82% accurate

ROC curves for RDI models with and without genotype and GSS from common rules systems



Model	AUC	Accuracy
RDI geno	0.88	82%
RDI no geno	0.86	78%
ANRS	0.72	66%
REGA	0.68	63%
Stanford db	0.71	67%
Stanford ms	0.72	68%

Larder BA *et al*. 49th ICAAC, 2009; H-894

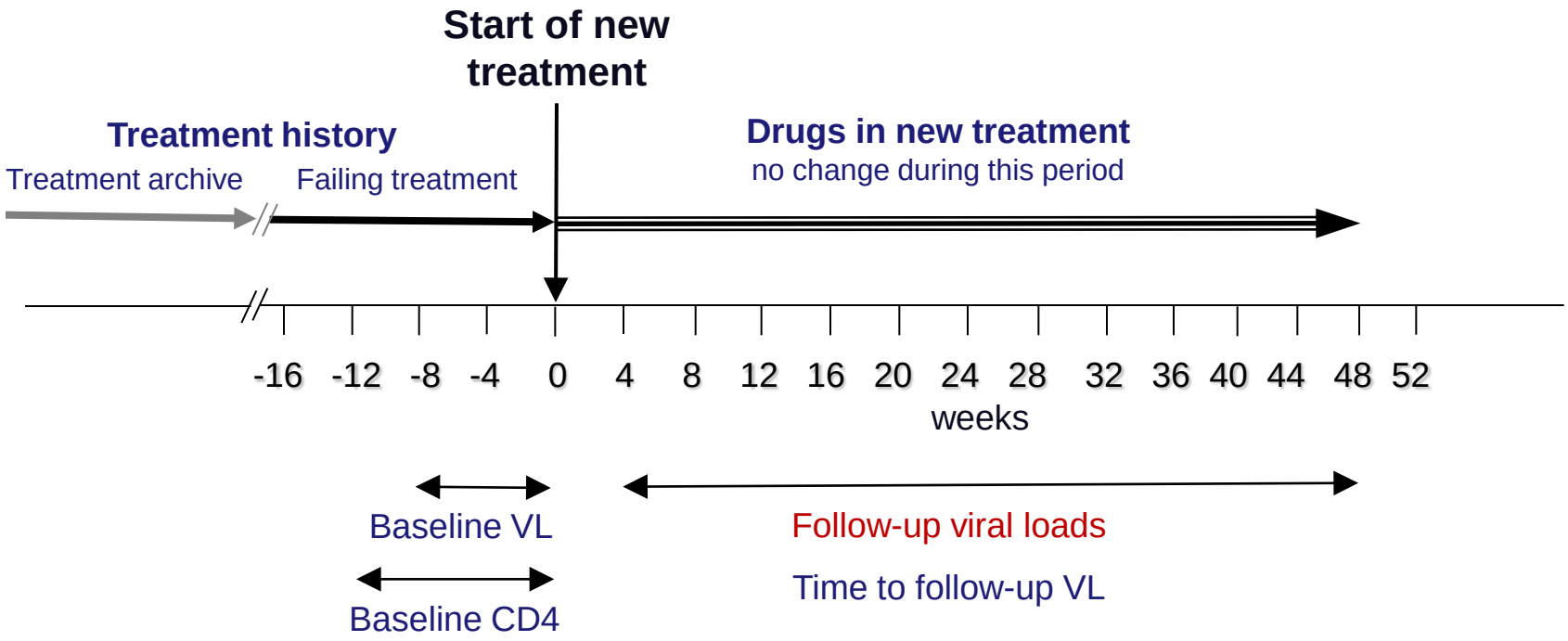
The issue of generalisability

- Our previous studies have shown that models are more accurate for patients from settings that are represented in the training data
- Our models are therefore evaluated not only during cross validation but with independent test sets and data from other settings
- Previous ‘no-genotype’ models were trained and tested with cases from ‘rich’ countries: Europe, Canada, USA, Australia, Japan
- ***How accurate would the RDI’s latest no-genotype models be for real cases from RLS?***

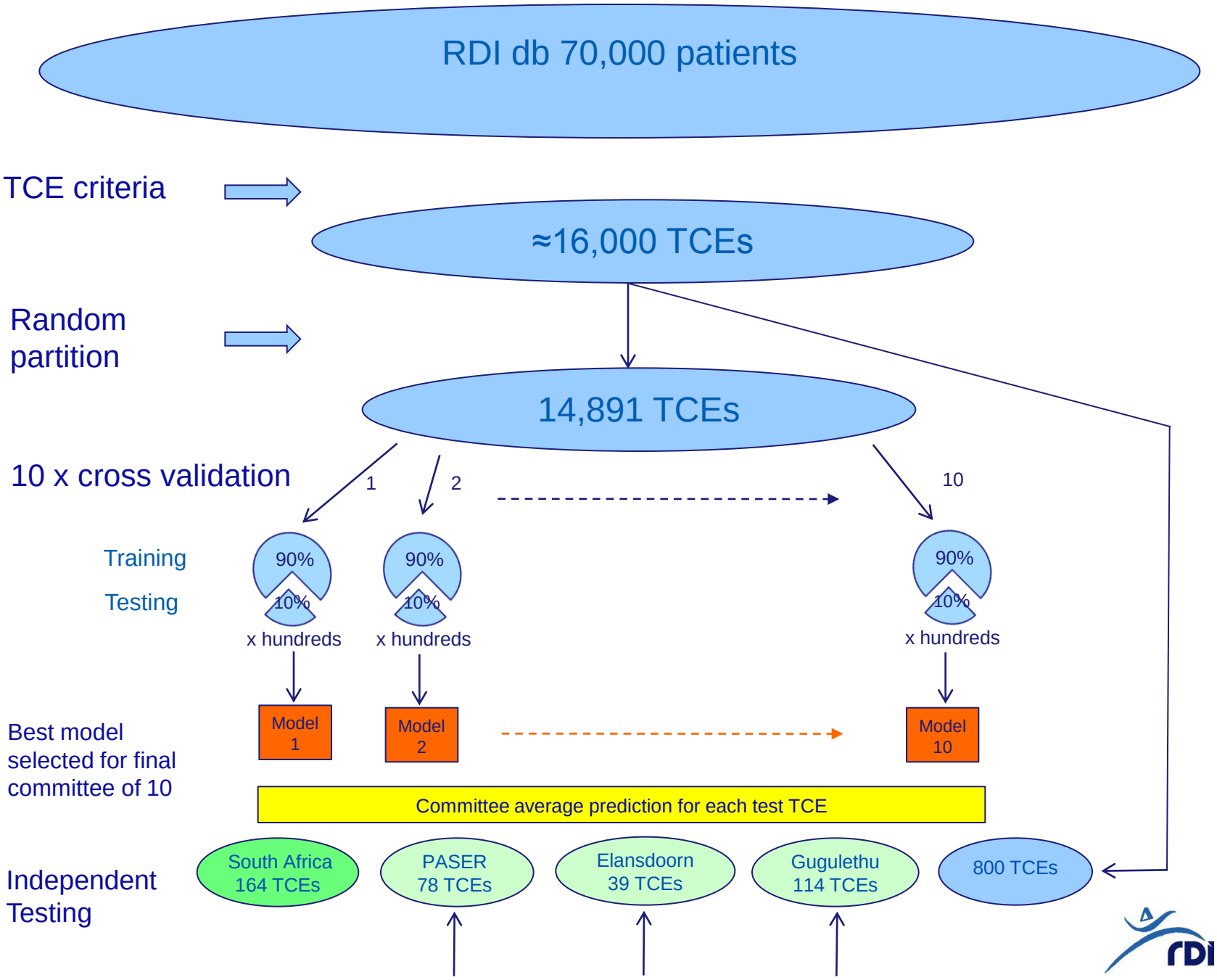
Current study objectives

1. To develop random forest (RF) models to predict virological response to cART without the use of genotype
2. To test these models with data from RLS
3. To use the models to identify potentially effective alternative regimens for cases of actual virological failure in RLS

The Treatment Change Episode (TCE)



Model output: Probability of the follow-up viral load <400 copies/ml


RDI db 70,000 patients
TCE criteria
≈16,000 TCEs
Random partition
14,891 TCEs
10 x cross validation
1
2
10
Training
Testing
90%
10%
x hundreds
Model 1
Model 2
Model 10
Best model selected for final committee of 10
Committee average prediction for each test TCE
Independent Testing
South Africa 164 TCEs
PASER 78 TCEs
Elansdoorn 39 TCEs
Gugulethu 114 TCEs
800 TCEs

Results

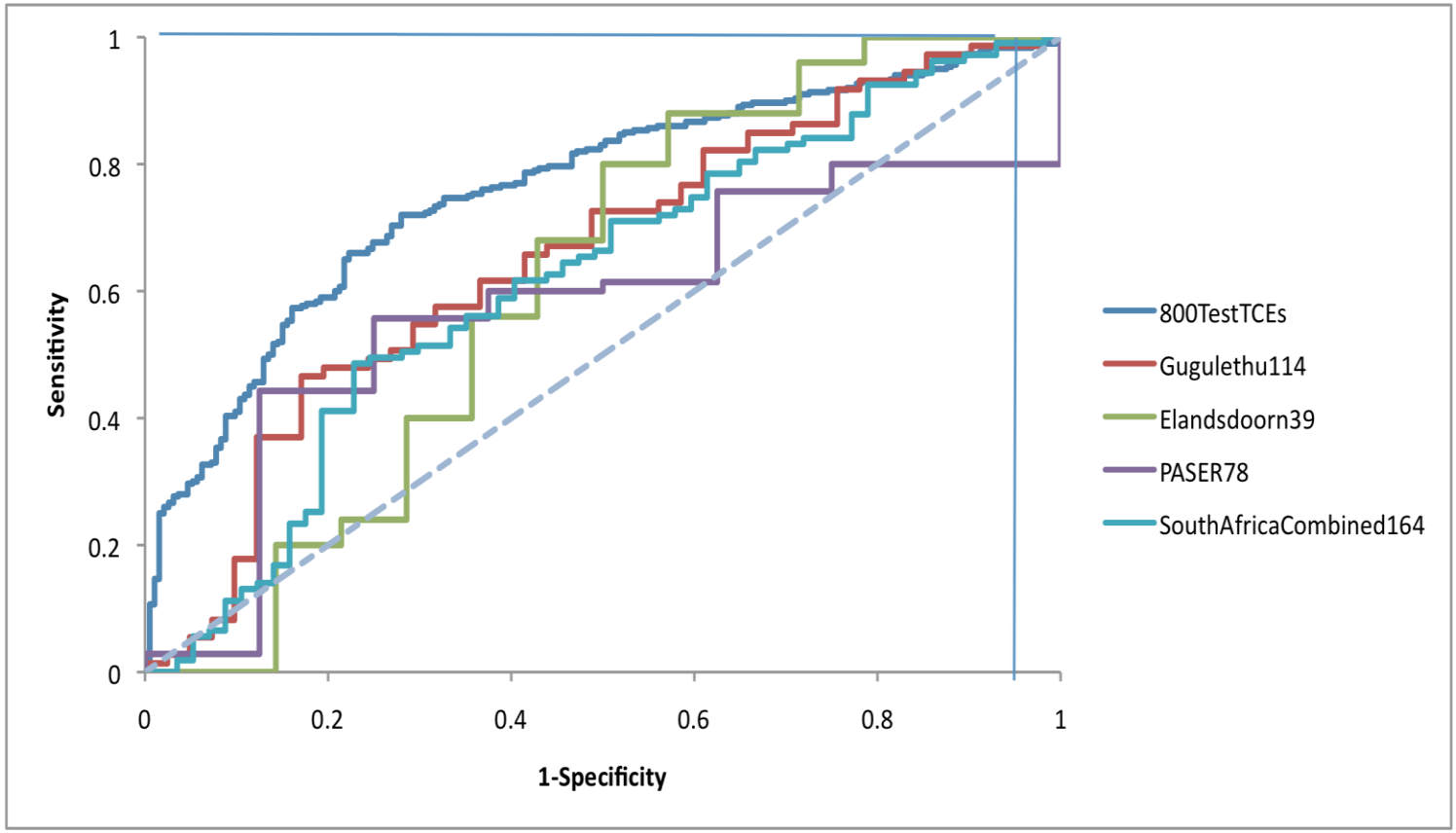
	Cross validation (n=14,891)	Test (n=800)	Gugulethu (n=114)	Elandsdoorn (n=39)	PASER (n=78)	South Africa (n= 164)
ROC AUC (95% CI)	0.77 (0.76, 0.78)	0.77 (0.73, 0.80)	0.65* (0.55, 0.76)	0.61 (0.40, 0.73)	0.58* (0.38, 0.77)	0.62** (0.53, 0.71)
Overall accuracy (95% CI)	72% (71%, 73%)	71% (68%, 74%)	67% (57%, 75%)	72% (55%, 85%)	71% (59%, 80%)	65% (57%, 72%)

Statistical comparison vs 800 test set using Delong's test for comparing ROC curves:

* Trend (P<0.1)

** Significant (P<0.01

ROC curves


Sensitivity
1
0.8
0.6
0.4
0.2
0
0
0.2
0.4
0.6
0.8
1
1-Specificity
800TestTCEs
Gugulethu114
Elandsdoorn39
PASER78
SouthAfricaCombined164

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* 3-drug regimens including one PI with no PIs in history

Performance of 2009 RF model trained and tested with cases with no PIs in their history

	Gugulethu (n=109)	Elandsdoorn (n=39)	PASER (n=73)	South Africa (n= 158)
ROC AUC	0.59	0.64	0.63	0.60
Overall accuracy	61%	62%	70%	60%

In silico analysis

- Cases from the RLS were identified where the new treatment failed and this was predicted by the models
- Models used the baseline data to predict responses to multiple alternative 3-drug regimens involving only those drugs in use in the centre(s)

	Gugulethu	Elandsdoorn	PASER	South Africa
No. of correctly predicted failures (total no. of failures)	26 (41)	7 (14)	6 (8)	34 (57)
No. (%) for which alternatives were found that were predicted to be effective	20 (77%)	6 (86%)	2 (33%)	27 (79%)

Conclusions

- RF models that do not require a genotype, trained with large datasets from resource-rich countries, are accurate predictors of virological response for cases from those countries
- These models are approximately 5% less accurate than is typical for models that use the genotype for their predictions
- The models are less accurate for cases from southern Africa but comparable to genotyping with rules-based interpretation
- The models have the potential to predict and avoid treatment failure by identifying effective, alternative, practical regimens
- We feel this approach has potential utility as an aid to the management of treatment failures in RLS.

Next steps

- A version of the RDI on-line treatment tool, HIV-TRePS, that does not require a genotype is being made available
- Data are being collected from RLS, and sub-Saharan Africa in particular, to develop region-specific models with the aim of maximising the accuracy of response prediction in these settings.

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