Uncertainty-Calibrated Prediction of Randomly-Timed Biomarker Trajectories with Conformal Bands

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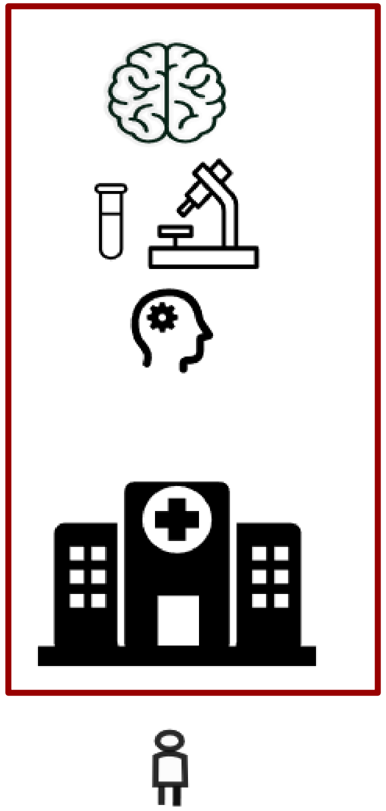
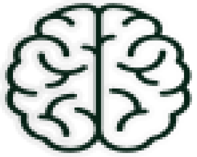
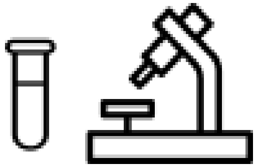
Biomarkers Guide Clinical Decisions



In healthcare, **biomarkers** drive the clinical decisions. Examples include:



Brain Biomarkers



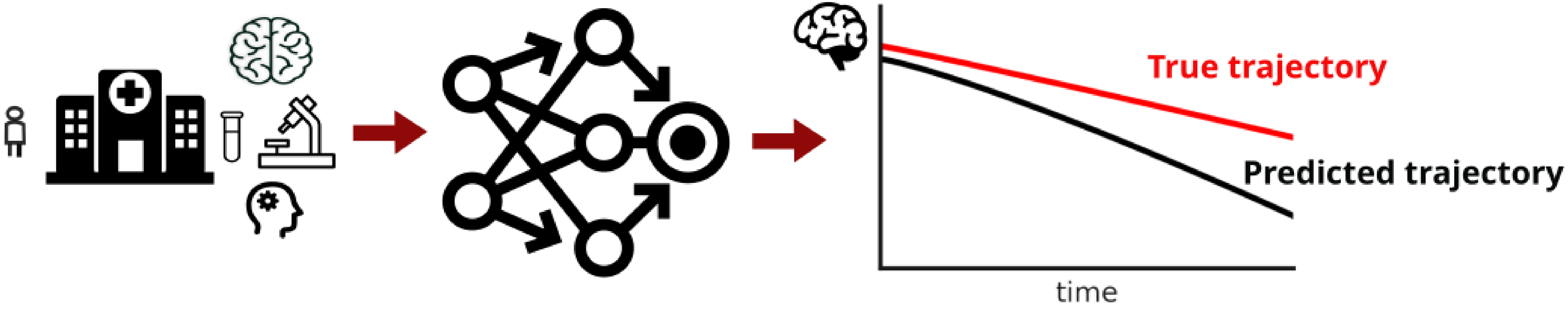
Blood Biomarkers

Cognitive Markers

An example of brain biomarker for Alzheimer's Disease is **Hippocampal volume**

First Visit

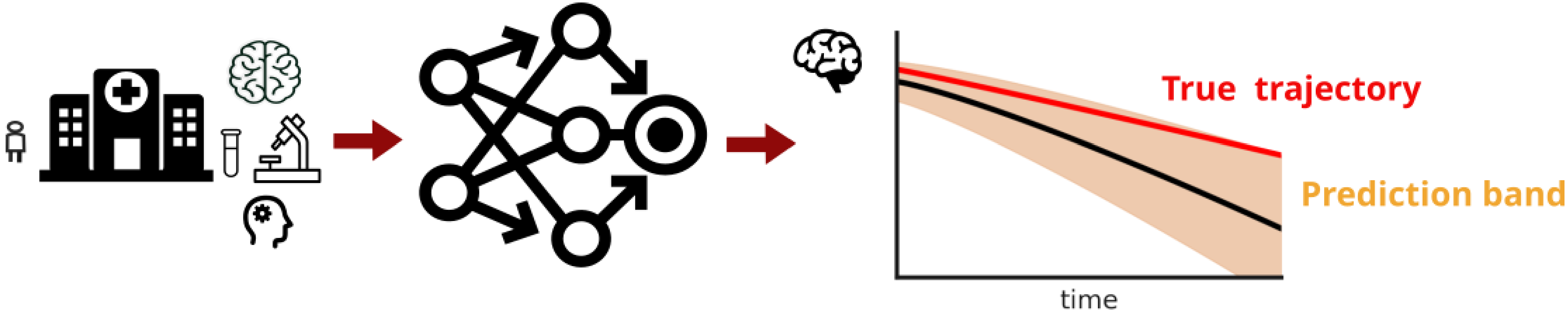
Learning Predictors of Biomarker



- Predictors of biomarker trajectories can make mistakes.
- Such mistakes lead to wrong decision making such as *no intervention for high-risk patients* and *unnecessary treatment for healthy patients*

We need uncertainty calibration of biomarker trajectory predictors.

Uncertainty-Calibrated Prediction of Biomarker Trajectories



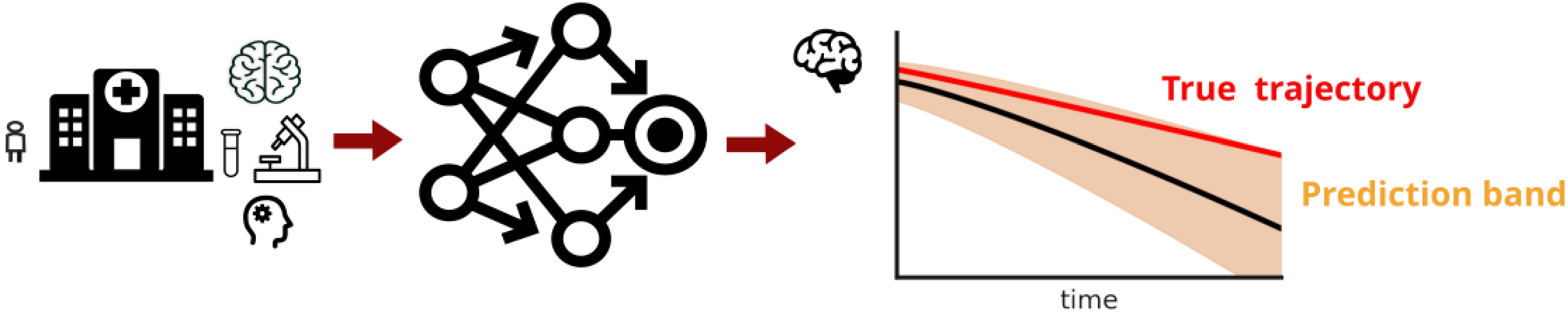
- Data from N subjects: $(X^{(1)}, Y^{(1)}, T^{(1)}), \ldots, (X^{(N)}, Y^{(N)}, T^{(N)})$

{Time in months of 1st, 2nd, 3rd clinical visit}

{MRI features, 64 years old, female, hippocampal volume on 1st clinical visit}

{Hippocampal volume on 2nd, 3rd, … clinical visit}

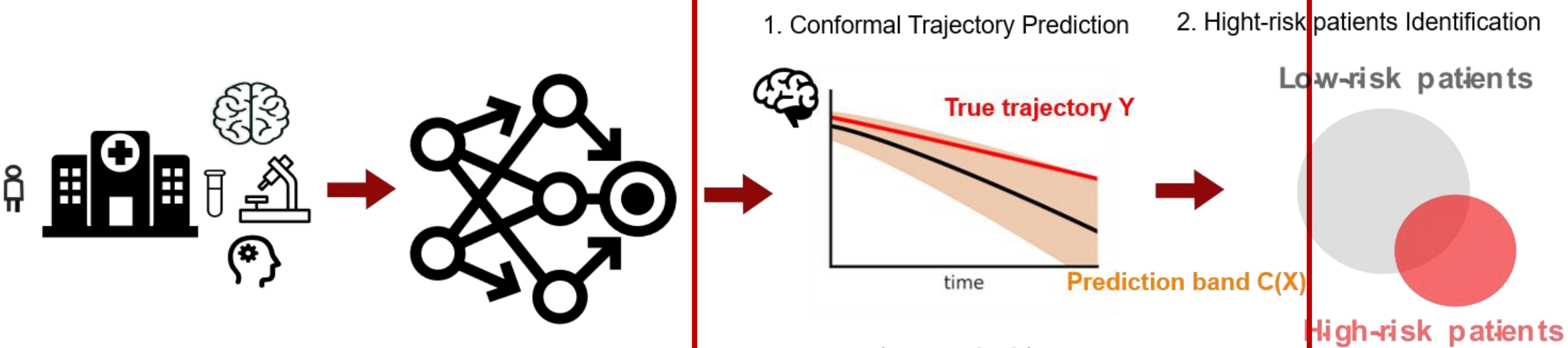
Uncertainty-Calibrated Prediction of Biomarker Trajectories



- Data from N subjects: $(X^{(1)}, Y^{(1)}, T^{(1)}), \ldots, (X^{(N)}, Y^{(N)}, T^{(N)})$
  - **Arbitrary** data distribution
- **Arbitrary** predictor yields predicted trajectories $\hat{Y}^{(1)}, \ldots, \hat{Y}^{(N)}$

Goal: Given a test subject input X, design a prediction band C(X) s.t.:
$\mathbf{P}(Y \in C(X)) \geq 1-\alpha$

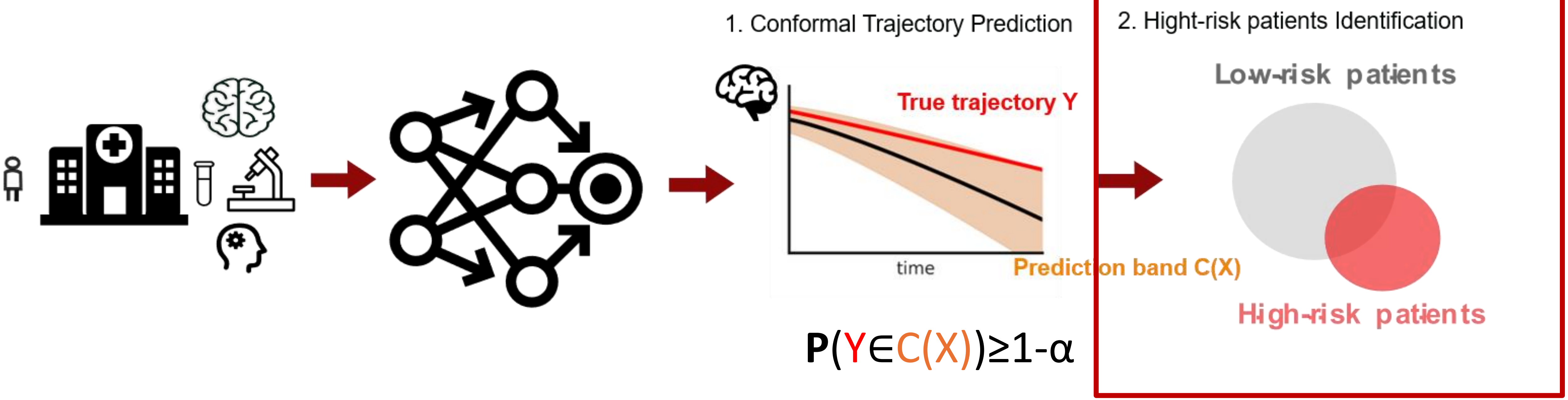
Contribution



$$P(Y \in C(X)) \geq 1-\alpha$$

1. We design conformal prediction bands of **randomly-timed** biomarker trajectories.

Contribution



1. We design conformal prediction bands of **randomly-timed** biomarker trajectories.

2. Using these prediction bands, we develop an **uncertainty-calibrated** method of identifying **high-risk patients**.

Prior Work

- Limiting assumptions on the data distribution and the predictor e.g., Gaussian noise, Bayesian models, …

Q1: What about **arbitrary** data distributions and predictors?

- Prior Conformal Prediction methods assume fixed-time trajectories

Q2: How to handle random clinical visits for each patient?

Conformal Prediction for Randomly-Timed Trajectories

- Patients visit the hospital at **random days**.
- **Idea:** Introduce a normalized non-conformity score:

$$R^{(i)} = \max_{t \in T^{(i)}} \frac{\boxed{\left| Y_t^{(i)} - \hat{Y}_t^{(i)} \right|}}{\sigma\left(\hat{Y}_t^{(i)}\right)}$$

Biomarker prediction error for patient i at time t

Conformal Prediction for Randomly-Timed Trajectories

- Patients visit the hospital at **random days**.
- **Idea:** Introduce a normalized non-conformity score:

$$R^{(i)} = \max_{t \in T^{(i)}} \frac{\left| Y_t^{(i)} - \hat{Y}_t^{(i)} \right|}{\boxed{\sigma\left(\hat{Y}_t^{(i)}\right)}}$$

Model-based (baseline) prediction uncertainty

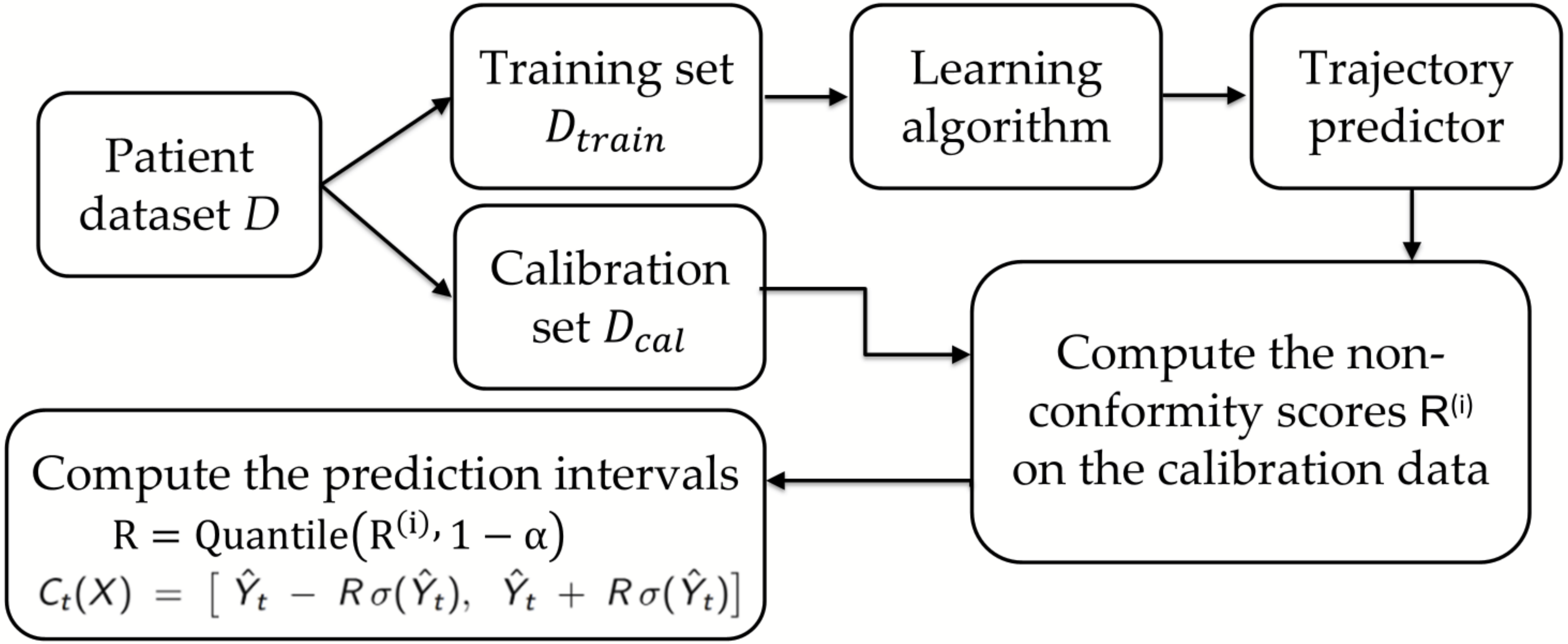
Conformal Prediction for Randomly-Timed Trajectories

- Patients visit the hospital at **random days**.
- **Idea:** Introduce a normalized non-conformity score:

Maximum over all timepoints

$$R^{(i)} = \boxed{\max_{t \in T^{(i)}}} \frac{\left| Y_t^{(i)} - \hat{Y}_t^{(i)} \right|}{\sigma\left(\hat{Y}_t^{(i)}\right)}$$

Conformal Prediction for Randomly-Timed Biomarker Trajectories



$$P\left(\forall t \in T: Y_t \in C_t(X)\right) \geq 1-\alpha$$

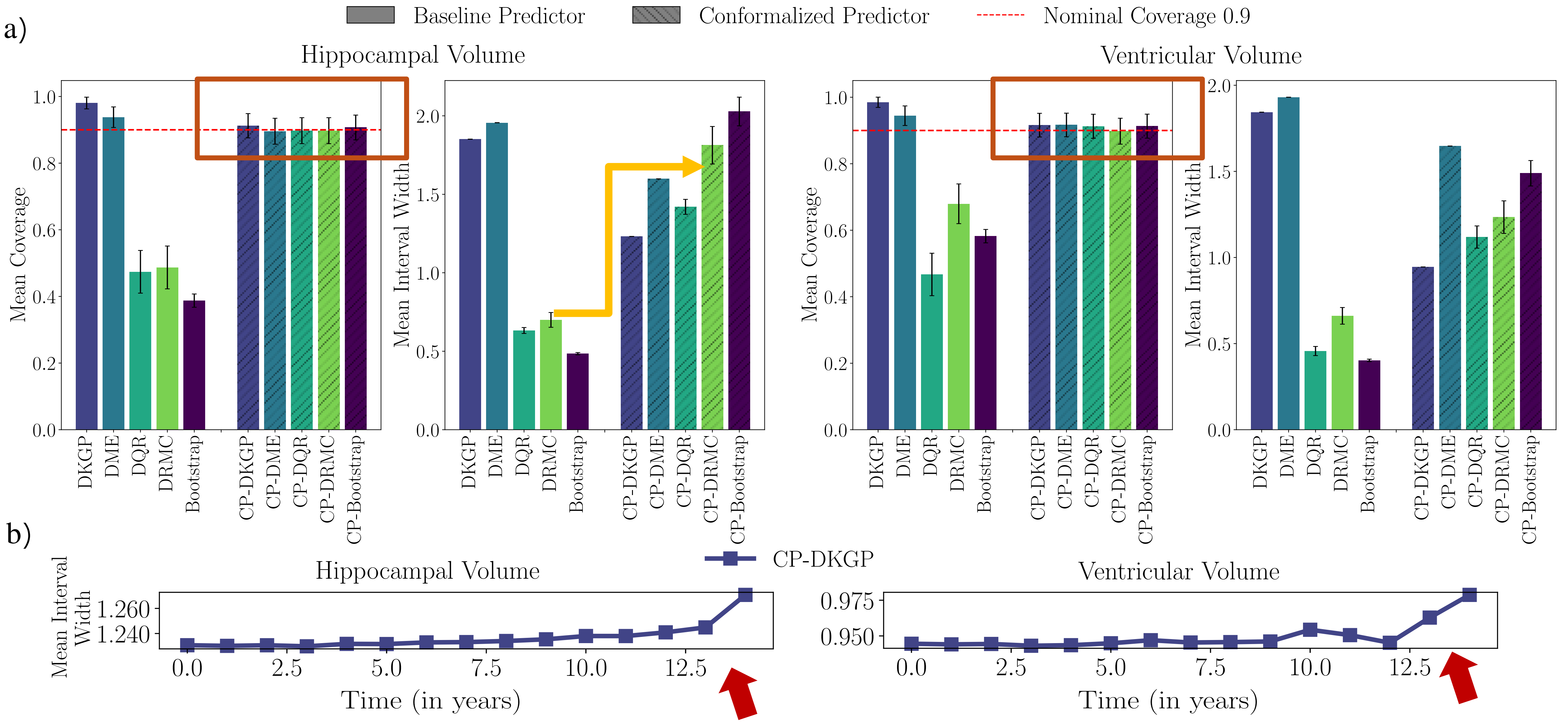
Conformal Prediction on Brain Biomarkers

- We apply our conformal method on **Hippocampal- and Ventricular-volume.**

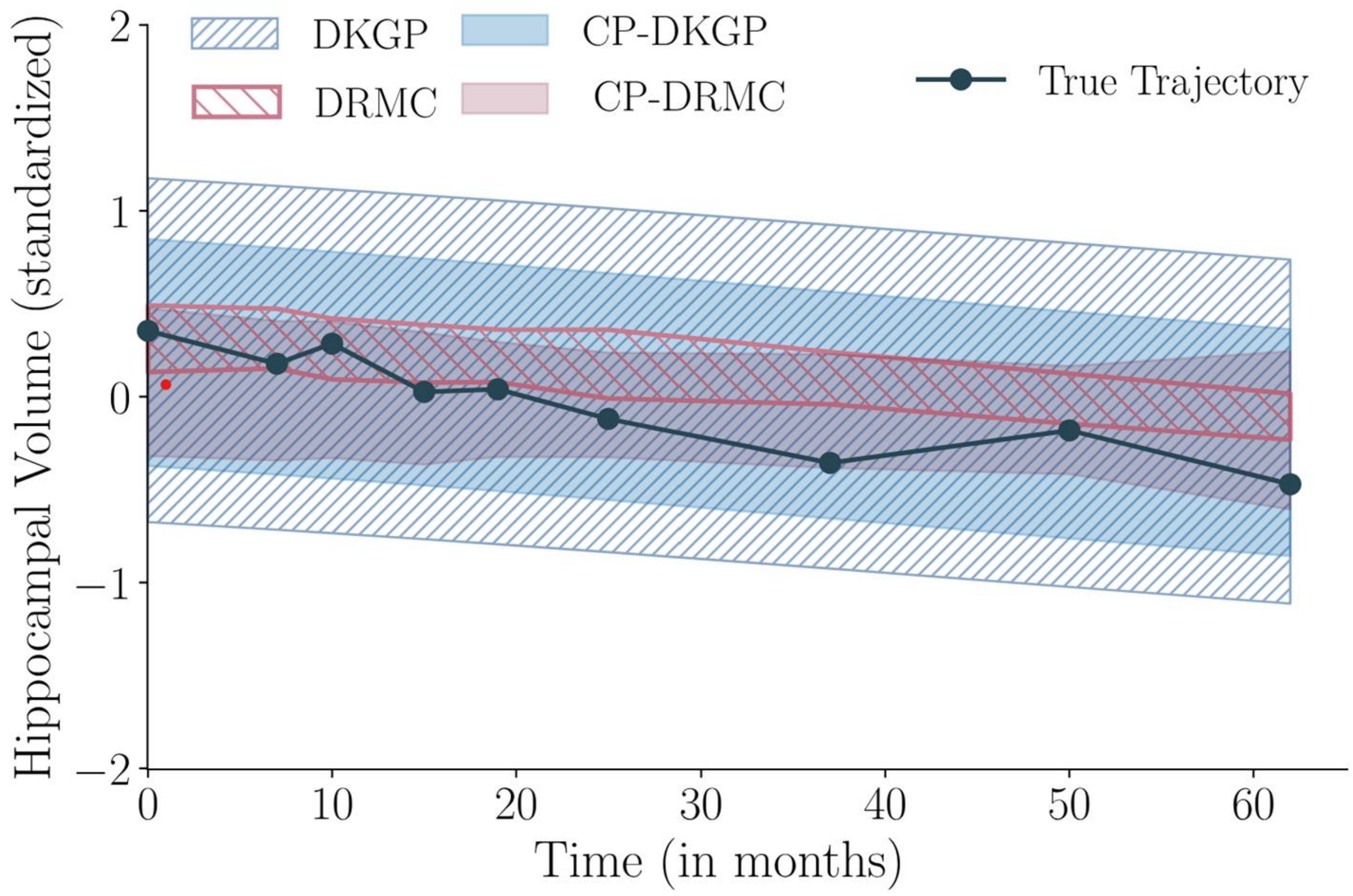
- For each biomarker, we use a dataset of **2,200 subjects**.

- We **conformalize** *baseline* and *state-of-the-art* predictors:
  - Deep Kernel Gaussian Process (DKGP) [5]
  - Deep Mixed Effects (DME) [1]
  - Deep Quantile Regression (DQR)
  - Bootstrap Deep Regression
  - Deep Regression with Monte Carlo Dropout

Results on Brain Biomarkers



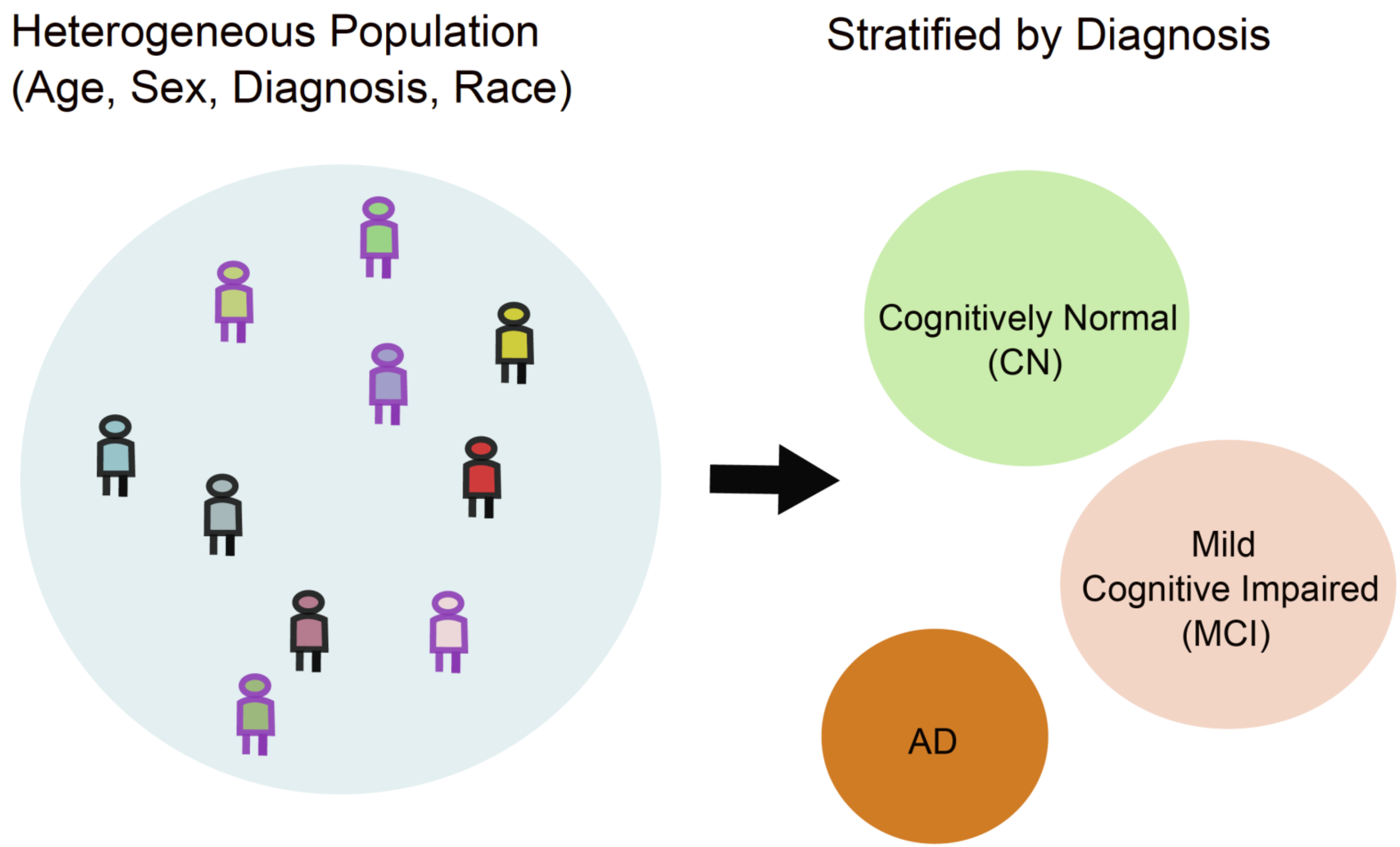
Qualitative Example



Our conformal prediction bands:

- Contain the true trajectories
- Are tight compared to baseline prediction bands

Group-Conditional Conformal Prediction



Idea:

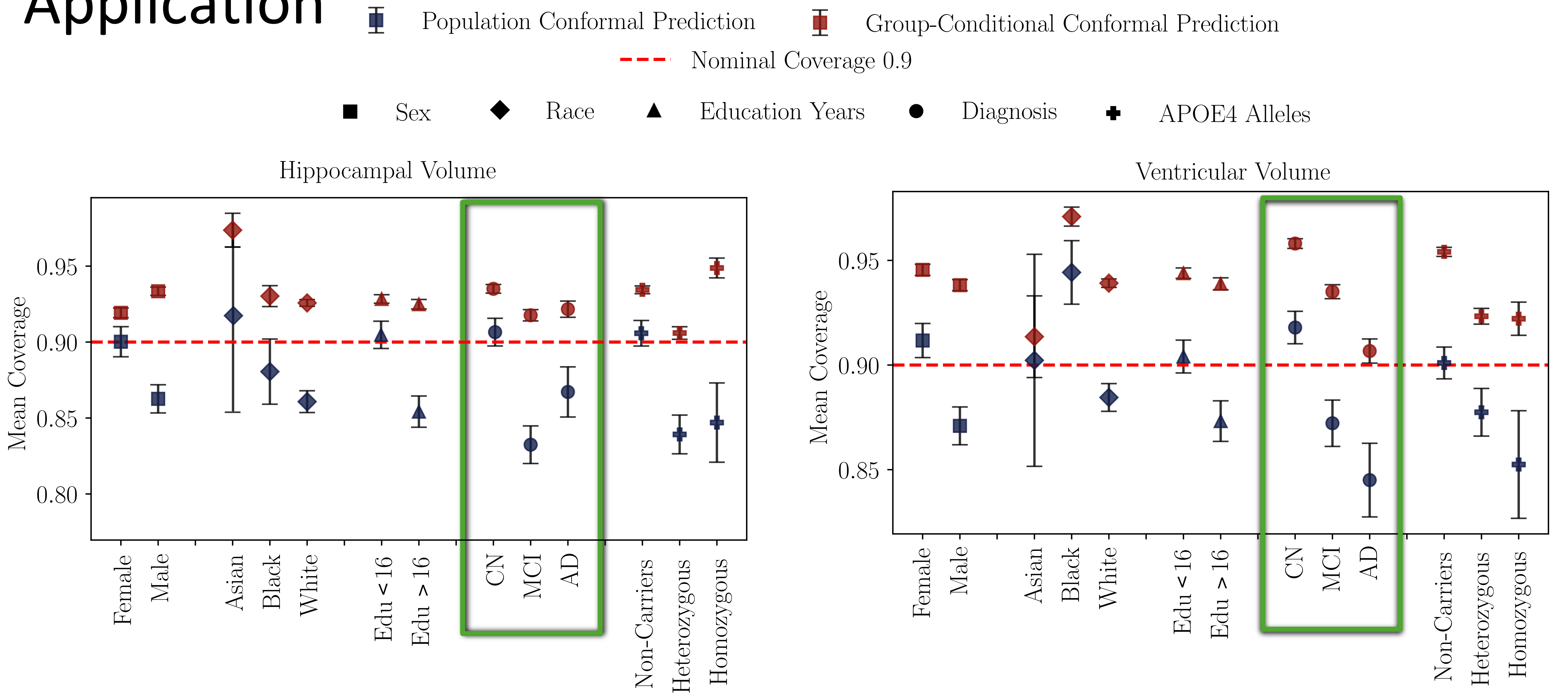
- Stratify calibration data by demographic and clinical covariates. E.g., age, sex, race, diagnosis
- Apply our conformal method within each group separately.

Example (Diagnosis):

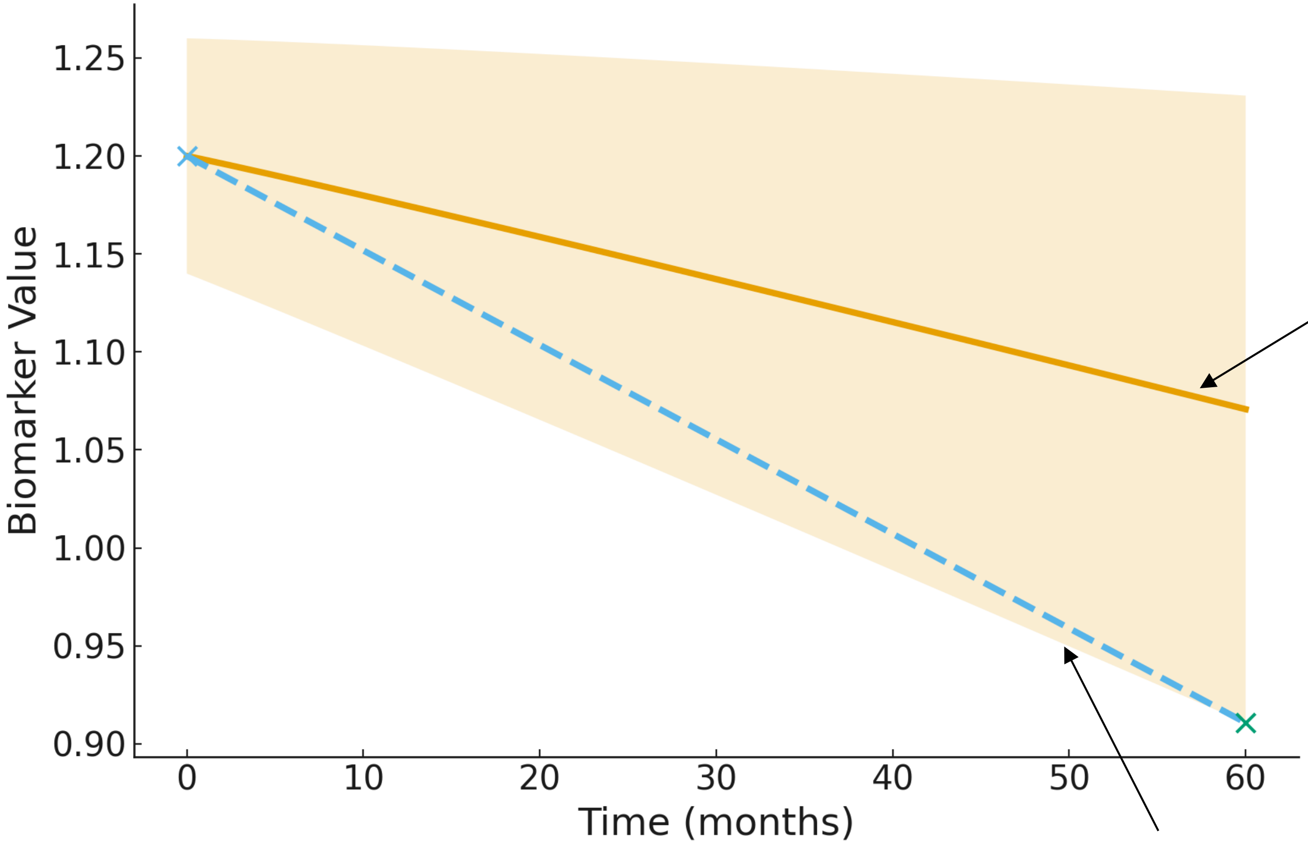
- **P**(Y∈C(X)|Group(X)=CN)≥1-α
- **P**(Y∈C(X)|Group(X)=MCI)≥1-α
- **P**(Y∈C(X)|Group(X)=AD)≥1-α

$$P\left(\forall\, t : Y_t \in C_t(X) \;\middle|\; G(X) = g\right) \geq 1 - \alpha.$$

Group-Conditional Conformal Prediction Application



Uncertainty-Calibrated Identification of High-Risk Subjects



Standard tool:

Predicted rate of change of the biomarker

$$\widehat{\mathrm{RoC}}^{(i)} = \frac{\widehat{Y}_{t_N}^{(i)} - Y_{t_0}^{(i)}}{t_N - t_0}$$

Our proposal:

Rate-of-change bound for the biomarker

$$\mathrm{RoCB}^{(i)} = \begin{cases} \dfrac{L_{t_N}^{(i)} - Y_{t_0}^{(i)}}{t_N - t_0} & \text{for decreasing biomarkers} \\ \dfrac{U_{t_N}^{(i)} - Y_{t_0}^{(i)}}{t_N - t_0} & \text{for increasing biomarkers} \end{cases}$$

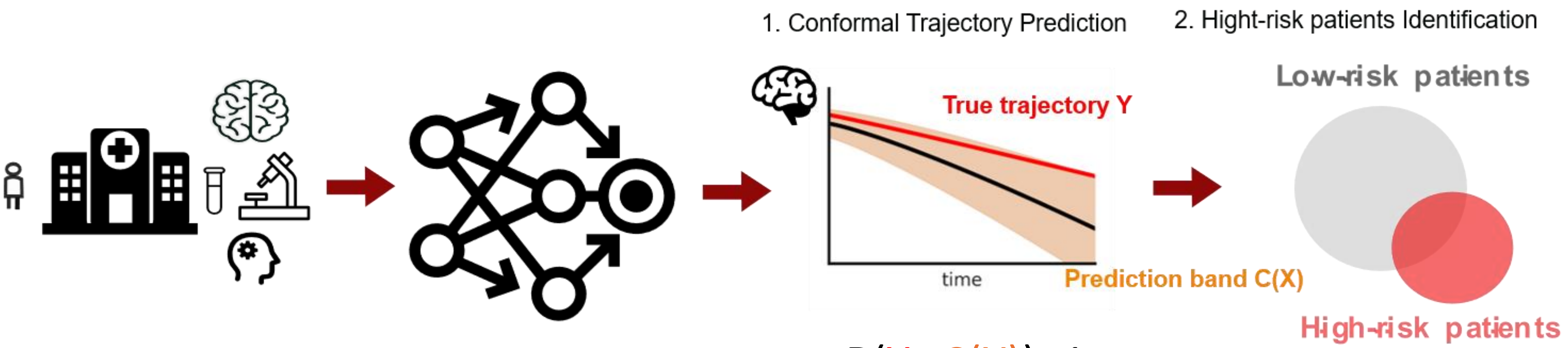
Uncertainty-Calibrated Identification of High-Risk Subjects

- **Task:** Identify MCI subjects that will probably convert to Alzheimer's Disease.
- **Method:** Compare the diagnostic success of the predicted rate of change and our rate-of-change bound.*

Method	Metric	$\tau^\star$	Precision	Recall	F_1
DRMC	$\widehat{\mathrm{RoC}}$	-0.006	**0.436** $\pm$ 0.022	0.671 $\pm$ 0.058	0.528 $\pm$ 0.023
	RoCB	-0.012	0.403 $\pm$ 0.022	**0.884** $\pm$ 0.058	**0.553** $\pm$ 0.023
CP–DRMC	$\widehat{\mathrm{RoC}}$	-0.006	**0.432** $\pm$ 0.022	0.740 $\pm$ 0.095	0.546 $\pm$ 0.024
	RoCB	-0.020	0.395 $\pm$ 0.022	**0.915** $\pm$ 0.095	**0.552** $\pm$ 0.024

* Identification based on Youden's optimized threshold.

Summary



$$P(Y \in C(X)) \geq 1-\alpha$$

Our **Code** is available at:

github.com/vatass/ConformalBiomarkerTrajectories

References

[1] Ingyo Chung, Saehoon Kim, Juho Lee, Kwang Joon Kim, Sung Ju Hwang, and Eunho Yang. Deep mixed effect model using gaussian processes: A personalized and reliable prediction for healthcare, 2019. URL https://arxiv.org/abs/1806.01551. 3, 5, 18

[2] Marco Lorenzi, Maurizio Filippone, Giovanni B. Frisoni, Daniel C. Alexander, and Sebastien Ourselin. Probabilistic disease progression modeling to characterize diagnostic uncertainty: Application to staging and prediction in Alzheimer's disease. NeuroImage, 190:56–68, April 2019. ISSN 1053-8119. doi: 10.1016/j.neuroimage.2017.08.059. URL http://dx.doi. org/10.1016/j.neuroimage.2017.08.059.

[3] Ognjen (Oggi) Rudovic, Yuria Utsumi, Ricardo Guerrero, Kelly Peterson, Daniel Rueckert, and Rosalind W. Picard. Meta-weighted gaussian process experts for personalized forecasting of ad cognitive changes. In Finale Doshi-Velez, Jim Fackler, Ken Jung, David Kale, Rajesh Ranganath, Byron Wallace, and Jenna Wiens, editors, Proceedings of the 4th Machine Learning for Healthcare Conference, volume 106 of Proceedings of Machine Learning Research, pages 181–196. PMLR, 09–10 Aug 2019. URL https://proceedings.mlr.press/v106/rudovic19a.html.

[4] Clement Abi Nader, Nicholas Ayache, Philippe Robert, and Marco Lorenzi. Monotonic Gaussian Process for spatio-temporal disease progression modeling in brain imaging data. NeuroImage, 205:116266, 2020. ISSN 1053-8119. doi: https://doi.org/10.1016/j.neuroimage.2019.116266. URL https://www.sciencedirect.com/science/article/pii/S1053811919308572.

[5] Vasiliki Tassopoulou, Fanyang Yu, and Christos Davatzikos. Deep Kernel Learning with Temporal Gaussian Processes for Clinical Variable Prediction in Alzheimer's Disease. In Antonio Parziale, Monica Agrawal, Shalmali Joshi, Irene Y. Chen, Shengpu Tang, Luis Oala, and Adarsh Subbaswamy, editors, Proceedings of the 2nd Machine Learning for Health symposium, volume 193 of Proceedings of Machine Learning Research, pages 539–551. PMLR, 28 Nov 2022. URL https://proceedings.mlr.press/v193/tassopoulou22a.html.3, 5, 7, 18

[6] Vasiliki Tassopoulou, Haochang Shou, and Christos Davatzikos. Adaptive shrinkage estimation for personalized deep kernel regression in modeling brain trajectories. In The Thirteenth International Conference on Learning Representations. 1, 3

[7] Kamile Stankeviciute, Ahmed M Alaa, and Mihaela van der Schaar. Conformal time-series forecasting. Advances in neural information processing systems, 34:6216–6228, 2021. 3, 19

[8] Matthew Cleaveland, Insup Lee, George J. Pappas, and Lars Lindemann. Conformal prediction regions for time series using linear complementarity programming. Proceedings of the AAAI Conference on Artificial Intelligence, 2024. 2, 3, 4, 19

[9] Xinyi Yu, Yiqi Zhao, Xiang Yin, and Lars Lindemann. Signal temporal logic control synthesis among uncontrollable dynamic agents withconformal prediction. arXiv preprint arXiv:2312.04242, 2023. 2, 3, 4, 19