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Predicting Declines in Lung Function with the US CF Registry: Impact of Initiating Highly Effective Modulator Therapy

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Presenter Disclosure

Grace C. Zhou, M.S.

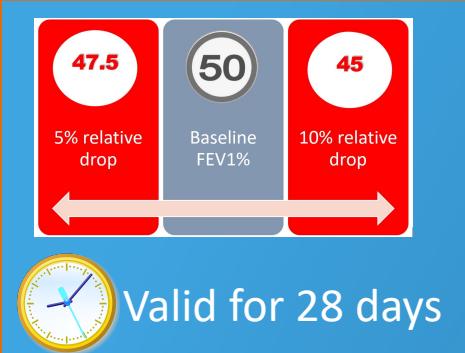
The following relationships exist related to this presentation:

- Cystic Fibrosis (CF) Foundation Research and Development Program, grant SZCZES20AB0
- Speaker and collaborators have no conflicts of interest to report

INTRODUCTION



- Highly effective modulator therapy (HEMT) continues to improve lung function trends in nearly 90% of CF patients
 - Elexacaftor, Tezacaftor, **Ivacaftor**

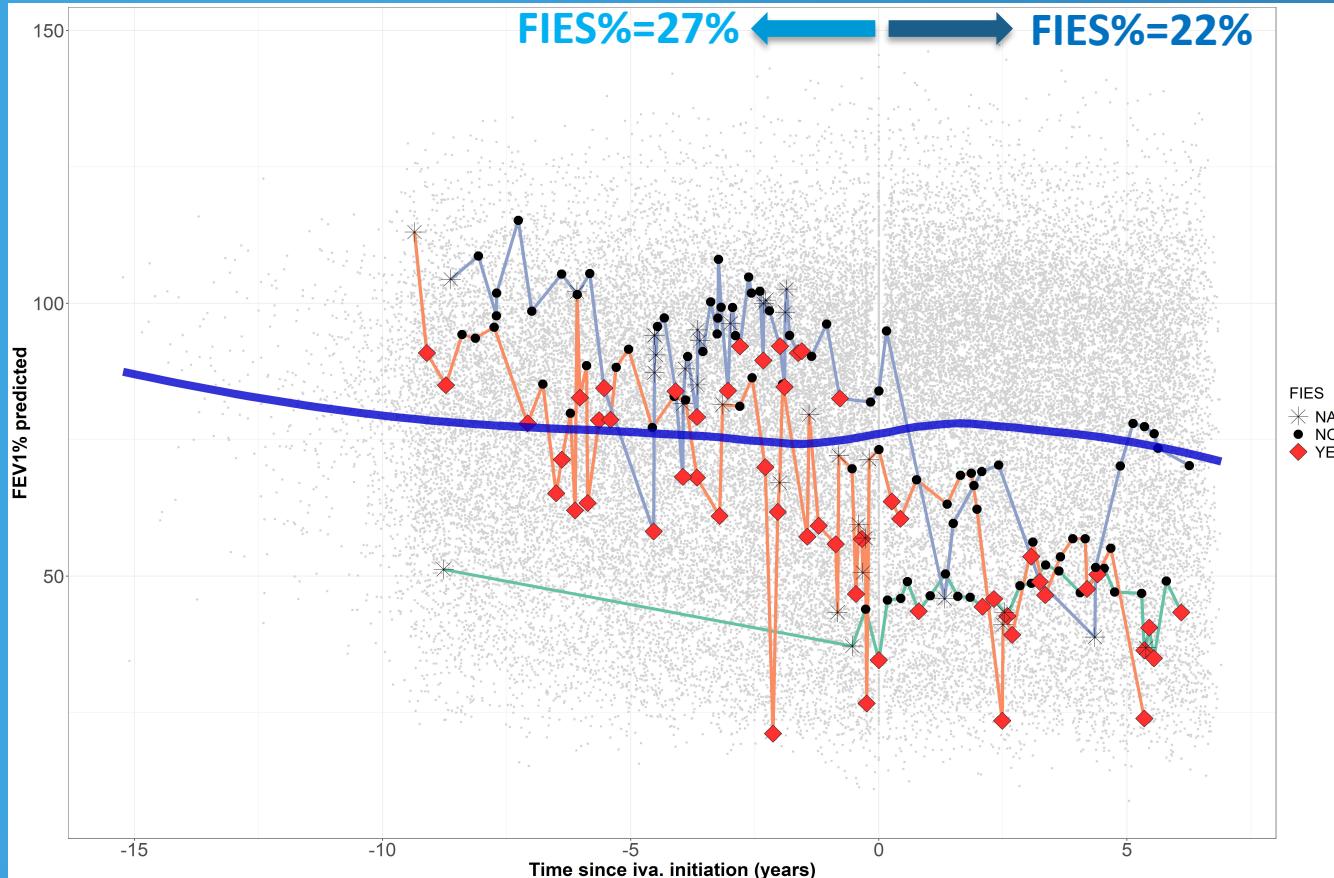


- Percent predicted forced expiratory volume in 1 second: FEV1% predicted
- FEV1-indicated exacerbation score: FIES (definition from Kris Petren, CFF)

OBJECTIVE

- How robust are predictions of lung function in post-HEMT era?
- How accurate are identifications of FIES events?

CFFPR DATA



Iva.
Age

21.58 (6.18-68.75)
years

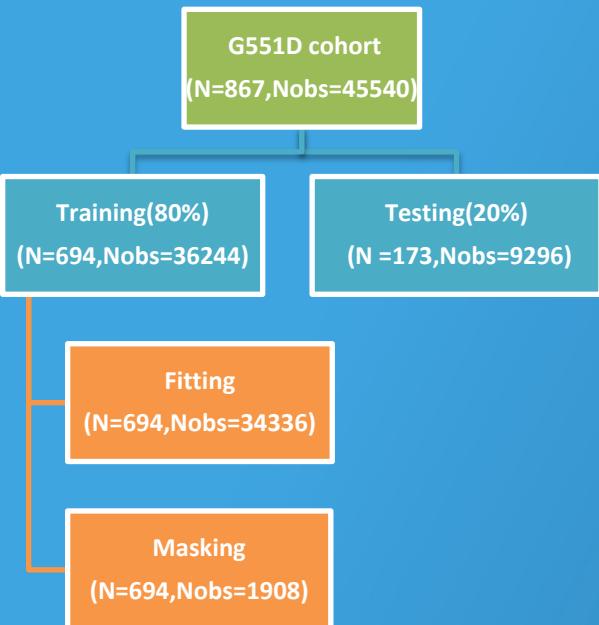
Follow
up

13.51 (1.04-15.96)
years

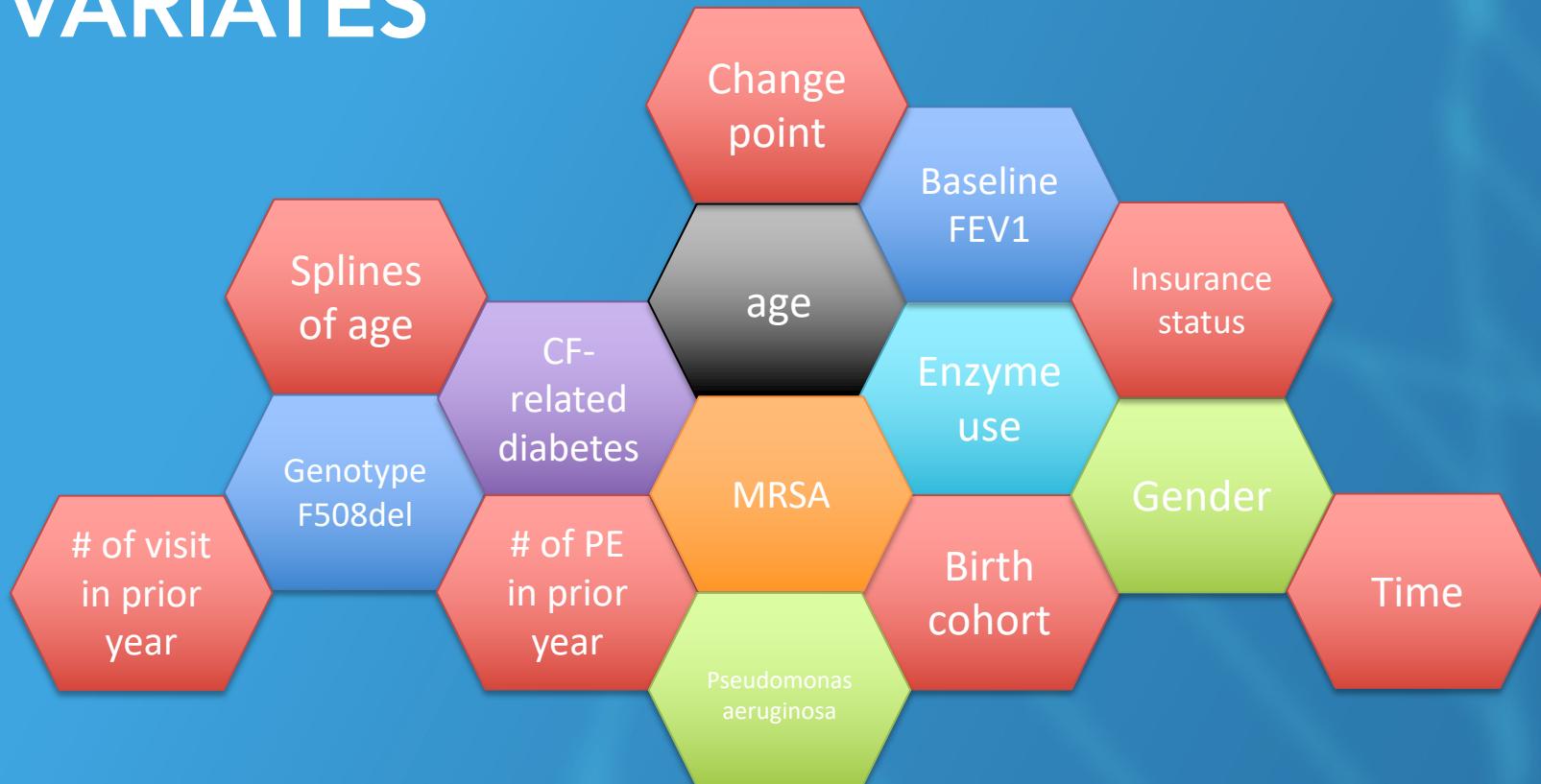
Figure 1: Observed FEV1(gray dots) against time with LOWESS smoothing curve(blue line) and FIES occurrence(shaped dots) for three random profiles(color lines)

STUDY COHORT

- Individuals with mutation G551D who ever started ivacaftor from 2012.1.1
- Aged over 6 y.o. from US CFFPR (2003-2018)
- At least ① encounter before initiation & at least ② encounters spanning at least 6 months after 30 days of the initiation
- Censored at lung transplantation, death or end of observed period



COVARIATES



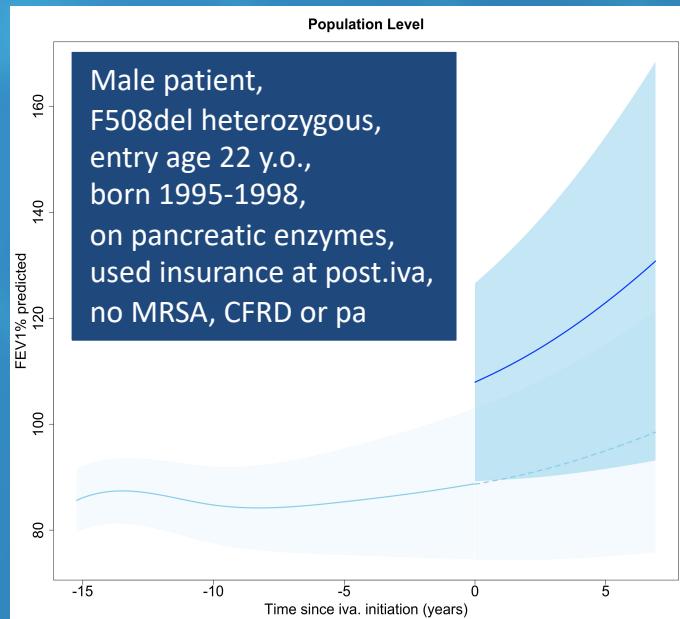
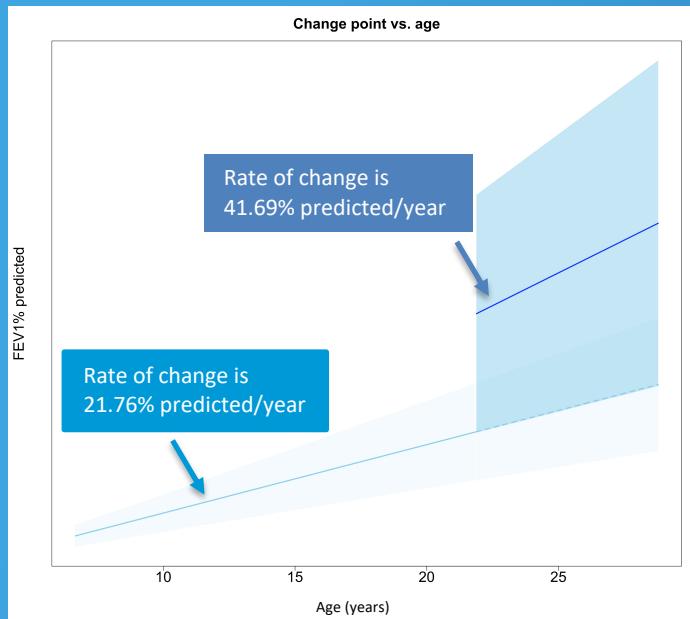
OPTIMAL MODEL

👍 Linear mixed effect model with nonstationary stochastic process

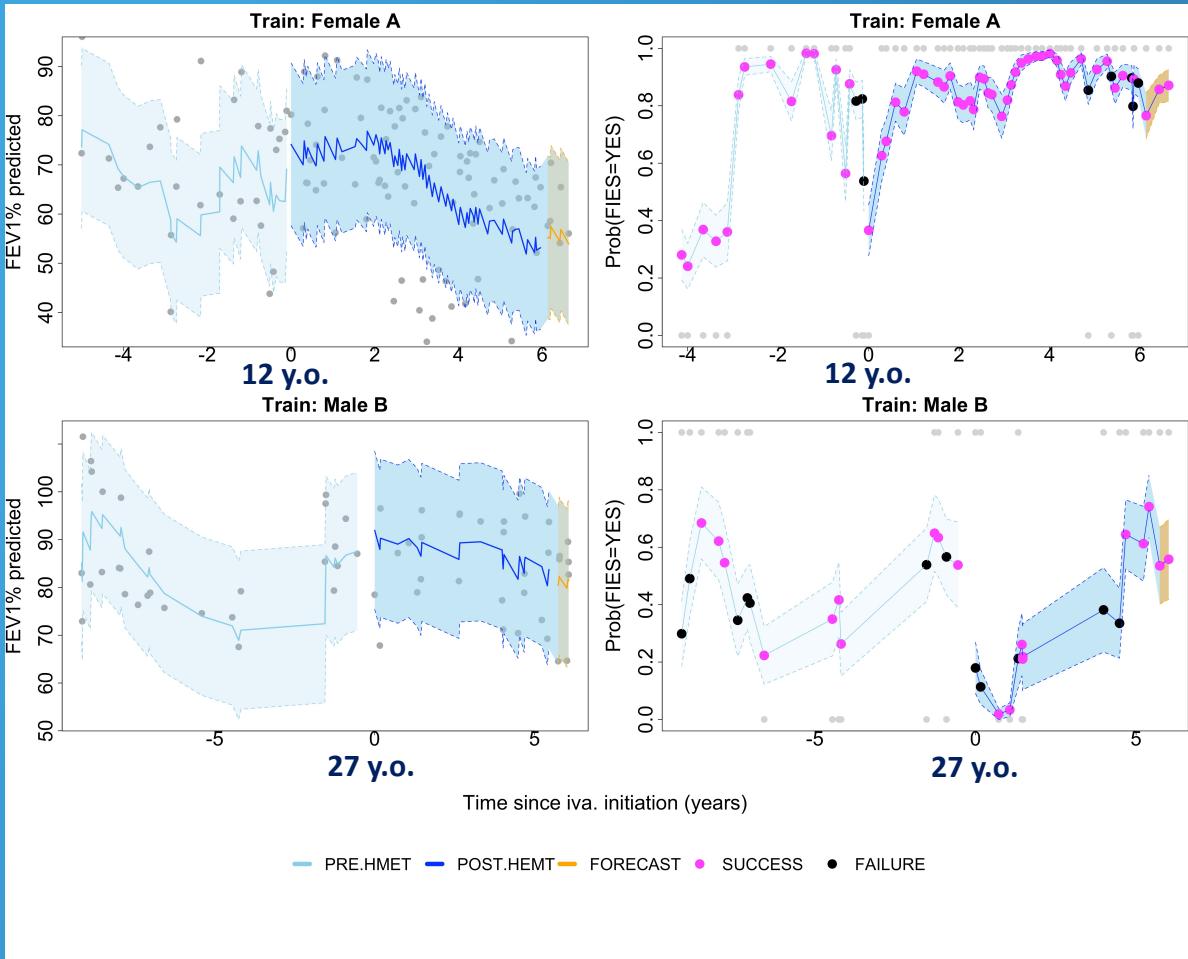
- Capture heterogeneous nature of FEV1 decline
- Monitor and predict probability of FIES events

👍 Impact of initiating HEMT

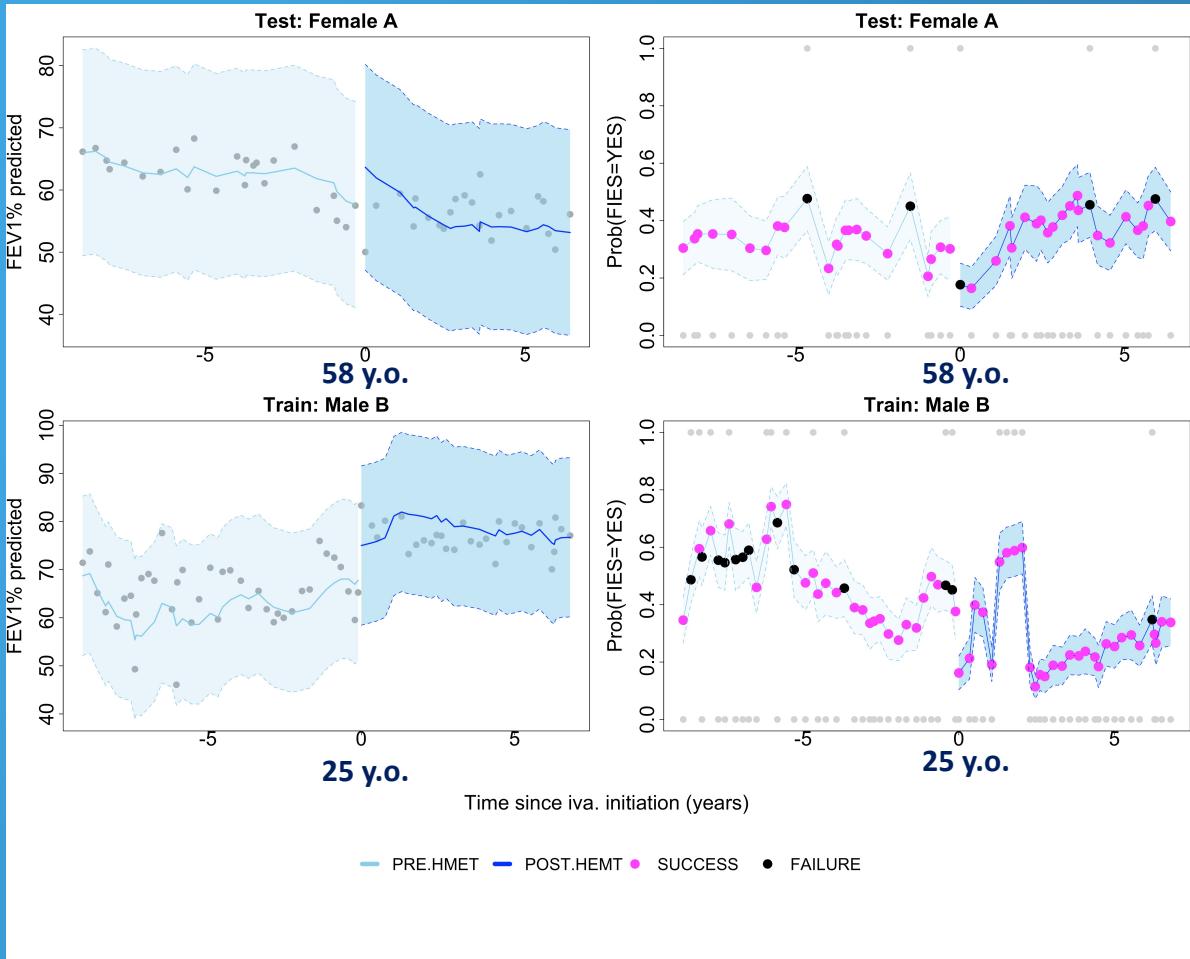
- The change point is a significant effect & corroborate positive impact of HEMT



PREDICTION 1



PREDICTION 2

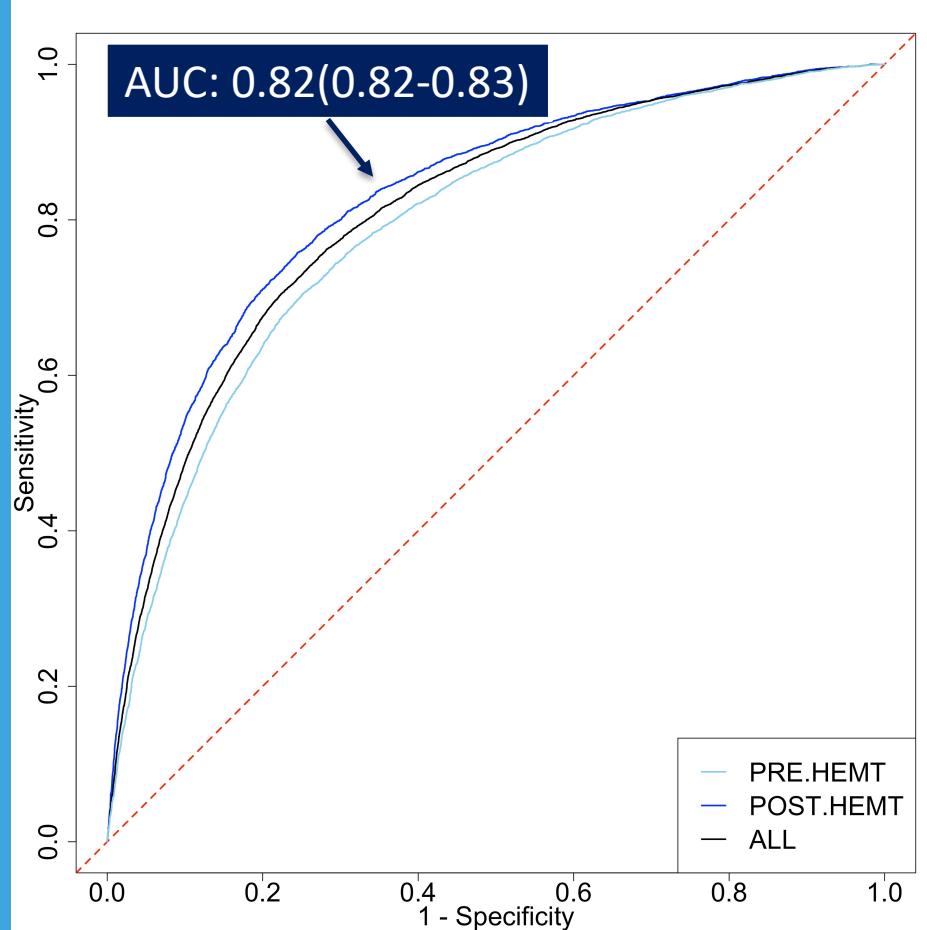


PREDICTIVE PERFORMANCE

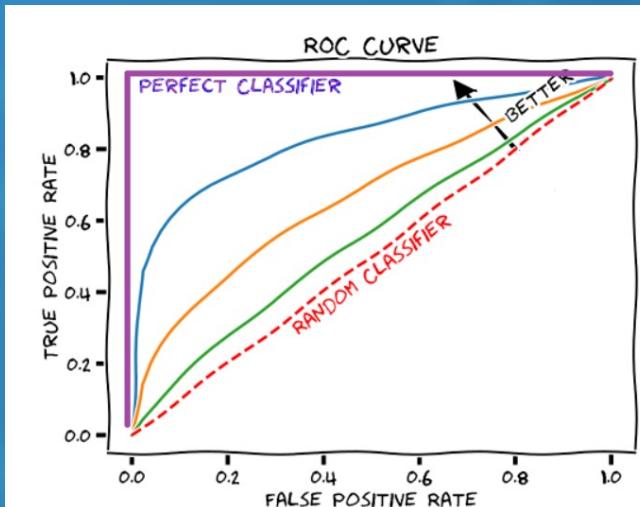
	FEV1% predicted:		FIES:	
	RMSE		AUC (95% CI)	
	PRE.IVA	POST.IVA	PRE.IVA	POST.IVA
FITTING(N=694)	8.31	7.7	0.79(0.78, 0.79)	0.82 (0.81,0.83)
FORECASTING(N=694)	NA	7.38	NA	0.87 (0.85, 0.89)
TESTING(N=173)	7.83	7.2	0.81(0.79, 0.82)	0.83 (0.81, 0.84)

- ✓ RMSE: Root Mean Square Error (😊 smaller)
- ✓ AUC: Area Under Curve (😊 larger)
- ✓ CI: Confidence Interval

FIES CLASSIFICATION



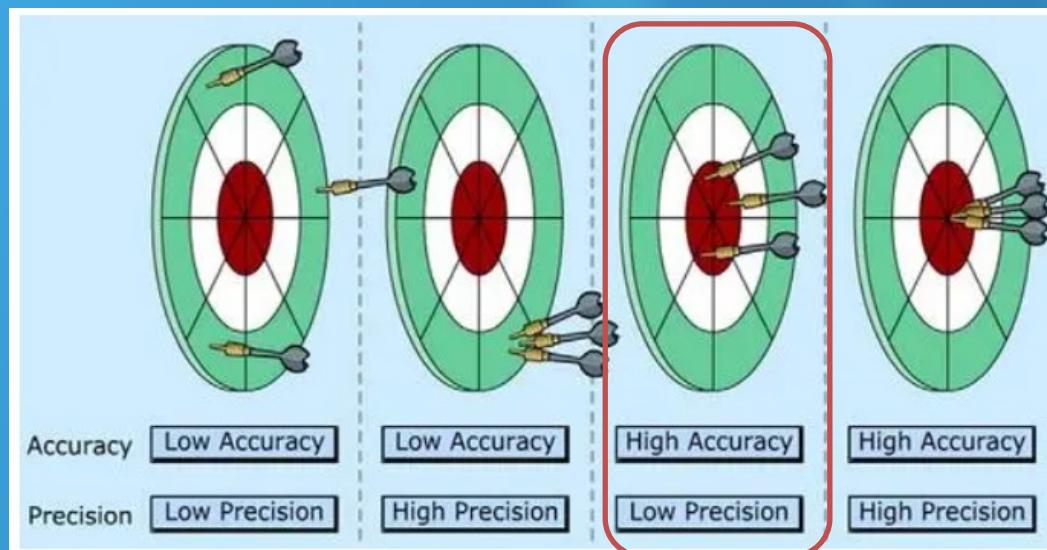
REFER TO



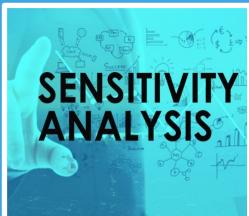
FIES CLASSIFICATION CONT.

	PRE.IVA	POST.IVA
ACCURACY	75%	80%
PRECISION	63%	62%

REFER TO



TAKEAWAYS



SENSITIVITY ANALYSIS

- New baseline
- Birth year
- 5-fold cross-validation



- Ivacaftor Only



- Measurement noise
- Other HEMTs
- Online tool

Shiny
from R Studio

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- R.D. Szczesniak, W. Su, C. Brokamp, H.K. Ruth, J.P. Pestian, M. Seid, P.J. Diggle, and J. Clancy. Dynamic predictive probabilities to monitor rapid cystic fibrosis disease progression. *Statistics in Medicine*, 39:740–756,2020