Prediction pathway for severe asthma exacerbations: a Bayesian Network analysis

Chandra Prakash Yadav, PhD, Atlanta Chakraborty, PhD, David B. Price, FRCGP, Laura Huey Mien Lim, MSc, Yah Ru Juang, Bsc, Richard Beasley, DSc, Mohsen Sadatsafavi, MD, PhD, Christer Janson, MD, PhD, Mariko Koh Siyue, MBBS, MRCP, FCCP, Eileen Wang, MD, MPH, Michael E. Wechsler, MD, David J. Jackson, MBBS, FRCP(UK), PhD, John Busby, PhD, Liam G. Heaney, MD, Paul E. Pfeffer, MRCP(UK), PhD, Bassam Mahboub, MD, Diahn-Warng Perng (Steve), MD, PhD, Borja G. Cosio, MD, PhD, Luis Perez-de-Llano, MD, PhD, Riyad Al-Lehebi, MD, FRCPC, Désirée Larenas-Linnemann, MD, FAAAAI, Dist.Intl.FACAAI, Mona S. Al-Ahmad, MD, FRCPC, Chin Kook Rhee, MD, PhD, Takashi Iwanaga, MD, PhD, Enrico Heffler, MD, PhD, Giorgio Walter Canonica, MD, Richard W. Costello, MB, MD, FRCPI, Nikolaos G. Papadopoulos, MD, PhD, FRCP, Andriana I. Papaioannou, MD, PhD, Celeste M. Porsbjerg, MD, PhD, Carlos A. Torres-Duque, MD· George C. Christoff, MD, PhD, MPH, Todor A. Popov, MD, PhD, Mark Hew, MBBS, PhD, FRACP, Matthew J. Peters, MD, PhD, Peter G. Gibson, MBBS, FRACP, Jorge Máspero, PhD, Celine Bergeron, MD, FRCPC, MSc, Saraid Cerda, MD, Elvia Angelica Contreras, MD, Wenjia Chen, PhD

Aim and Methods

Rationale

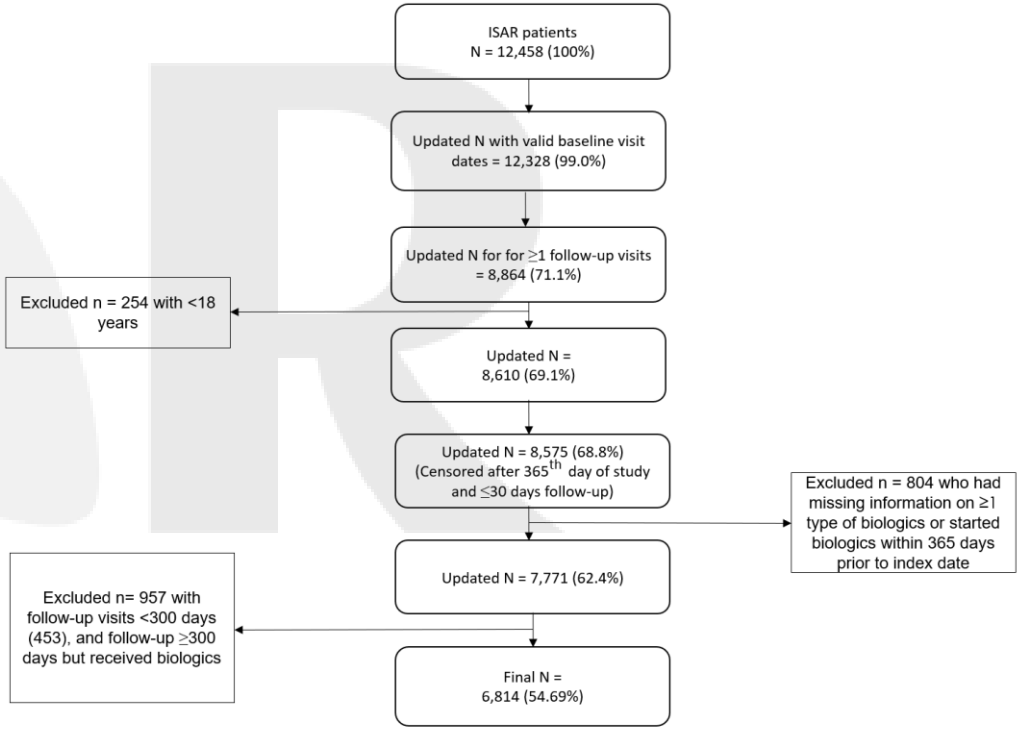
Accurate risk prediction of exacerbations is pivotal in severe asthma management. Multiple risk factors are at play, but the pathway of risk prediction remains unclear.

Aim

To examine how key clinical predictors interact to drive severe asthma exacerbations, supporting more informed clinical decision-making.

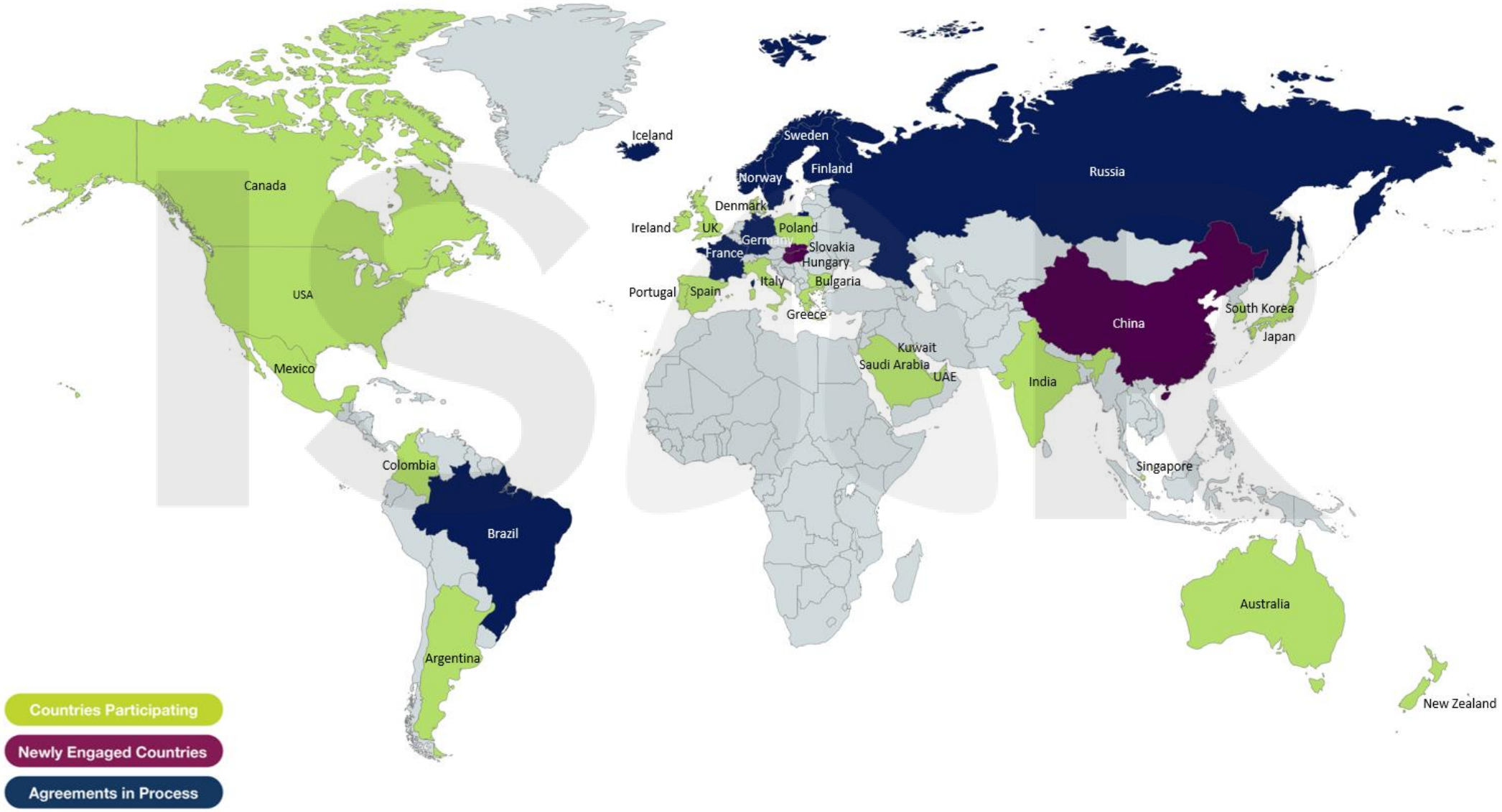
Methods

- **Data source:** The International Severe Asthma Registry (ISAR).
- **Study population:** Patients ≥ 18 years of age who did not initiate any biologics before the baseline visit.
- **Statistical analyses:** A Bayesian network, developed using expert input and machine learning, identified key pathways leading to severe exacerbations, complemented by an influence diagram incorporating decision and utility nodes.



Flow diagram of the International Severe Asthma Registry cohort

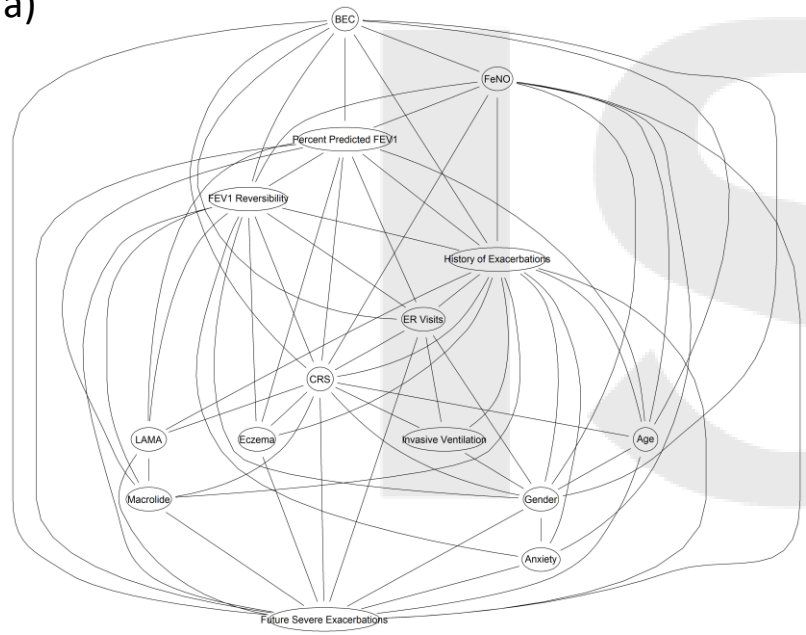
ISAR participating countries



The comprehensive local neighborhood network of relevant predictors

Bayesian Network plots: Initial parent-child relationship learnt, machine learning with expert knowledge integration, and final model with clinically relevant arcs.

a)



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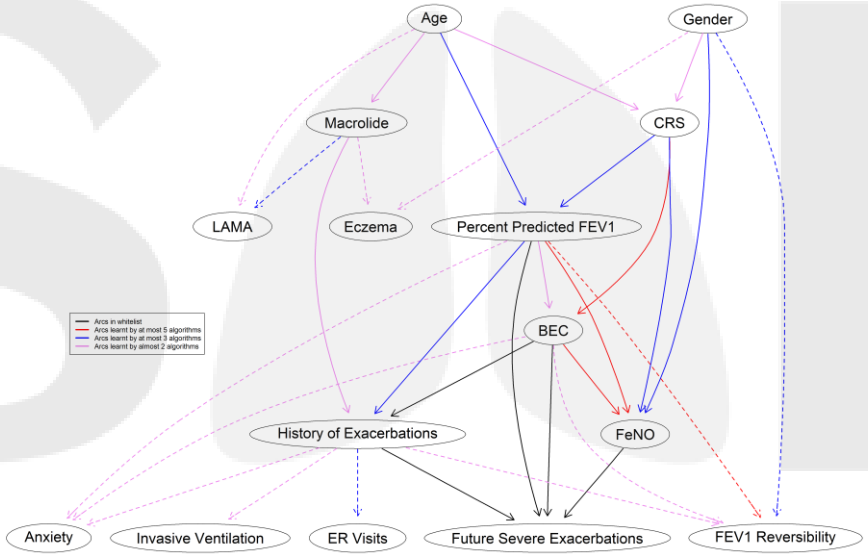


c)

Key Predictors Identified:

- Among 14 LASSO-selected predictors, those most connected included prior severe exacerbations, FeNO, % predicted FEV1, BEC, macrolide use, and CRS.

Machine-Learned BN Structure:

- ML algorithms consistently identified core arcs—CRS → BEC, FEV1 → FeNO, and BEC → FeNO—while predictors like anxiety and ER visits were peripheral.

Final Expert-Tuned BN (2 main pathways):

- (1) CRS impacts biomarkers and lung function leading to future exacerbations;
- (2) Age and sex influence CRS and macrolide use, which in turn affects exacerbation risk.

Model discrimination was moderate in 10-fold cross-validation and leave-one-country-out cross-validation, and model calibration was high in train-test data.

Validation results

Performance Metrices	10-fold cross-validation	
AUC[1]	0.65	
Specificity[2]	0.75	
Precision[3]	0.50	
Recall[4]	0.50	
Accuracy[5]	0.63	
Calibration using 70:30 train-test data		
Calibration intercept[6]	risk of ≥1 severe exacerbations	0.130
	risk of ≥2 severe exacerbations	-0.018
Calibration slope[6]	risk of ≥1 severe exacerbations	0.804
	risk of ≥2 severe exacerbations	0.949

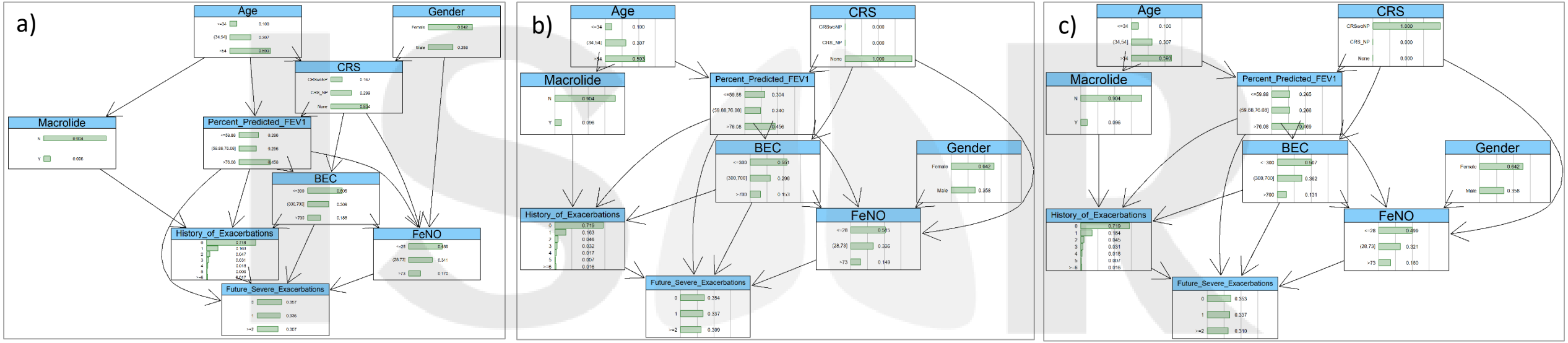
1. AUC (Area Under the Curve): Range between 0 and 1, indicating the probability that a classifier will rank a randomly chosen positive instance higher than a randomly chosen negative one.
2. Specificity: Range between 0 and 1, measures the proportion of actual negatives that are correctly identified as such by the classifier.
3. Precision: Range between 0 and 1, denotes the proportion of true positive predictions among all positive predictions made by the classifier.
4. Recall: Range between 0 and 1, represents the proportion of actual positives that are correctly identified as such by the classifier.
5. Accuracy: Range between 0 and 1, measures the proportion of correct predictions made by the classifier over all predictions.
6. A calibration slope near 1 and an intercept close to zero signify well-calibrated models with accurate risk estimation across different individuals.

Findings

- **Discrimination**: The BN model showed moderate predictive performance with AUCs of 0.65 (10-fold CV) and 0.62 (leave-one-country-out), supported by consistent specificity, precision, recall, and accuracy.
- **Calibration**: Good model calibration was observed with calibration intercepts (0.130, -0.018) and slopes (0.804, 0.949) in test data for predicting ≥1 and ≥2 severe exacerbations.

The conditional probability table of BN and counterfactual analysis

Conditional probability and counterfactual analysis



Conditional Probability Plot:

- BN model estimates future severe exacerbation risk based on levels of upstream clinical predictors.

CRS Impact Simulation:

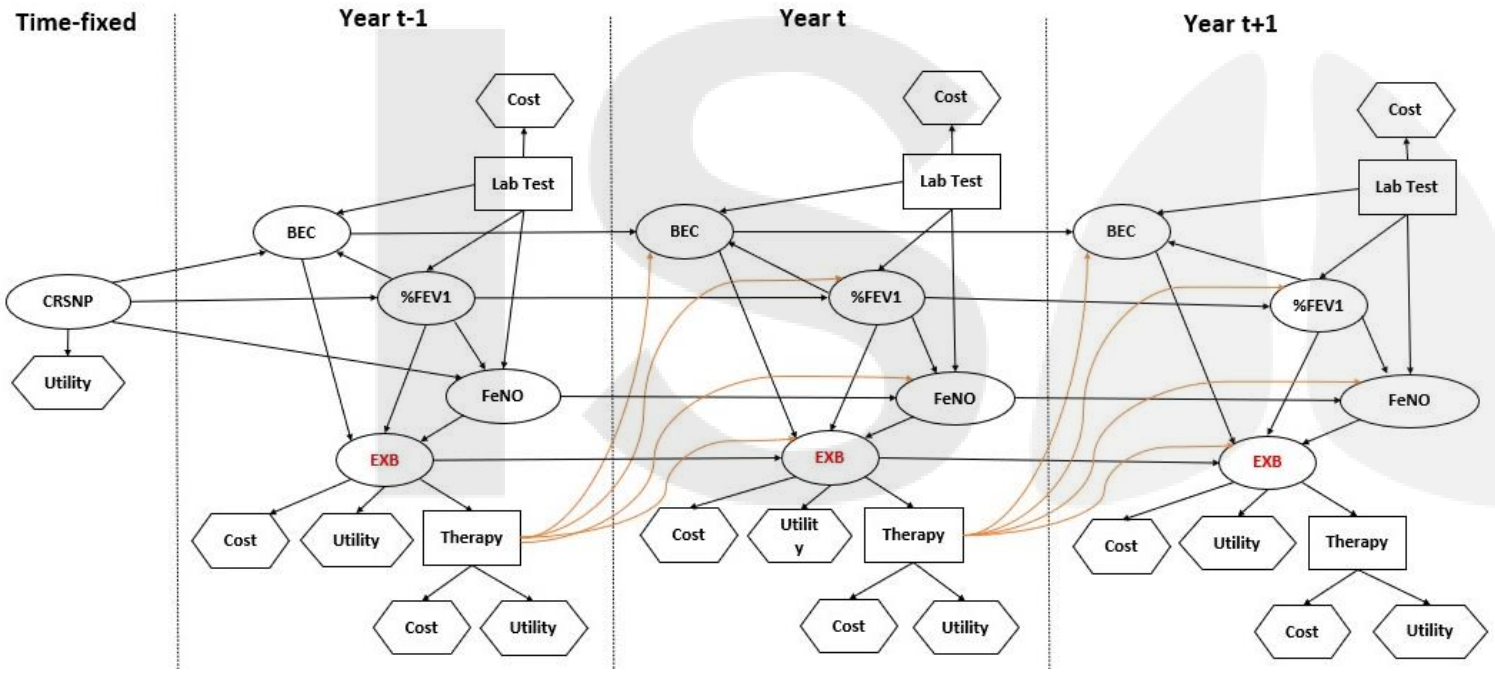
- Changing CRS status to “CRS without NP” alters downstream biomarkers (FEV1, BEC, FeNO).

Prediction Shift:

- These biomarker shifts lead to a change in the predicted probability of future severe exacerbations.

Influence diagram identified CRS-Biomarker-Lung Function pathway driving future severe exacerbations

Influence diagram integrating nodes, cost and utility



Findings

- **CRS–Biomarker–Lung Function Pathway**: The model emphasized how CRS influences biomarkers (BEC, FeNO) and lung function (% predicted FEV1), which drive the transition from current to future severe exacerbations.
- **Treatment Decision Integration**: Treatment was modeled as a decision node post-exacerbation, influencing biomarker levels and lung function, thus shaping future exacerbation risk and costs.

Conclusions

- An essential prediction pathway of severe exacerbation was identified, which involves the **influence of CRS on the immediate predictors** of risk transition from current to future severe asthma exacerbations.

- The BN also reveals heterogeneity in predicted risks, with **macrolide use linked to the transition from past to future exacerbations** through a separate, non-T2 pathway.

- Findings provided significant insights for **asthma risk prediction** and potentially support the **cost-effectiveness analysis** of interventions related to T2 inflammations and/or CRS.