Prediction of treatment outcomes in rheumatoid arthritis

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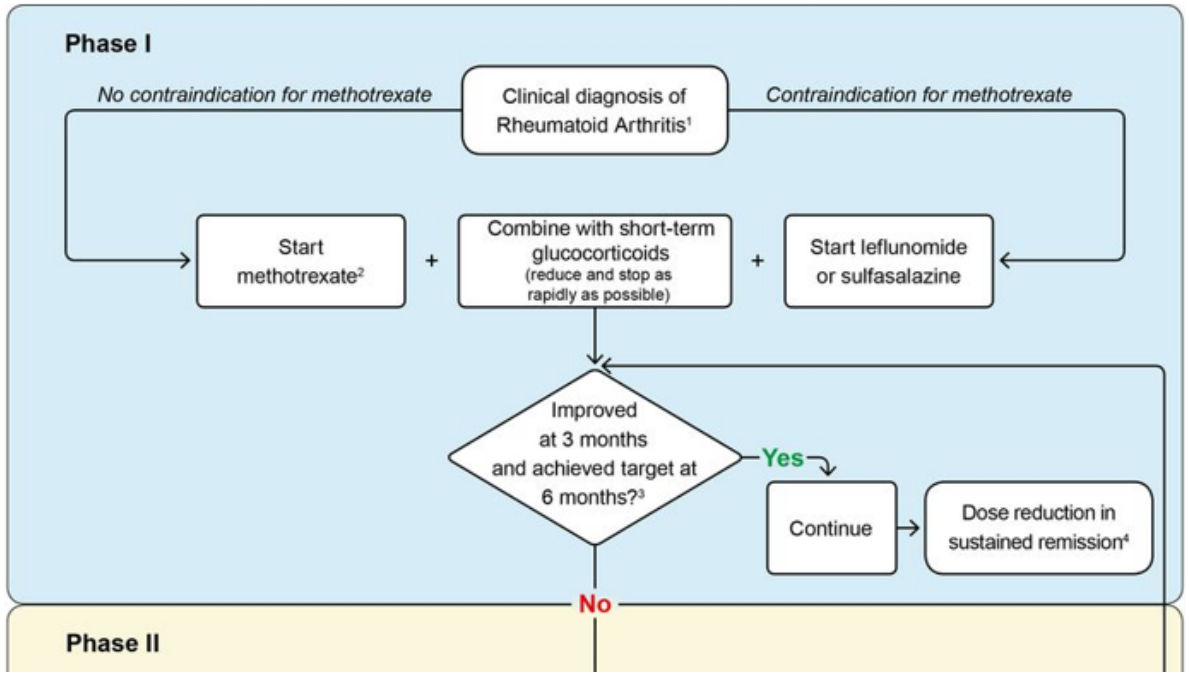
Rheumatoid arthritis (RA)

- Chronic, inflammatory disease
  - → Destruction of joints
  - → Comorbid conditions
- Complex disease
  - → Genetics+environment
- Prevalence 1%

Treatment algorithm for RA



Josef S Smolen et al. Ann Rheum Dis 2023;82:3-18

Treatment response in RA

- Important to get disease under control quickly
  - → Stop inflammatory cycle
  - → Prevent joint damage
  - → Decrease risk for comorbidities

- We need to predict who will benefit from a treatment to not loose time!

Aim

Can we predict who will stay on MTX in DMARD monotherapy 1 year after treatment start?

ACR Open Rheumatol. 2021 Jul; 3(7): 457–463.
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PMCID: PMC8280803
PMID: 34085401

ACR Open Rheumat

What Is the Persistence to Methotrexate in Rheumatoid Arthritis, and Does Machine Learning Outperform Hypothesis-Based Approaches to Its Prediction?

Helga Westerlind,[✉ 1] Mateusz Maciejewski, [2] Thomas Frisell, [1] Scott A Jelinsky, [2] Daniel Ziemek, [2] and Johan Askling [1]

‣ J Intern Med. 2025 Apr 6;297(6):693–701. doi: 10.1111/joim.20087

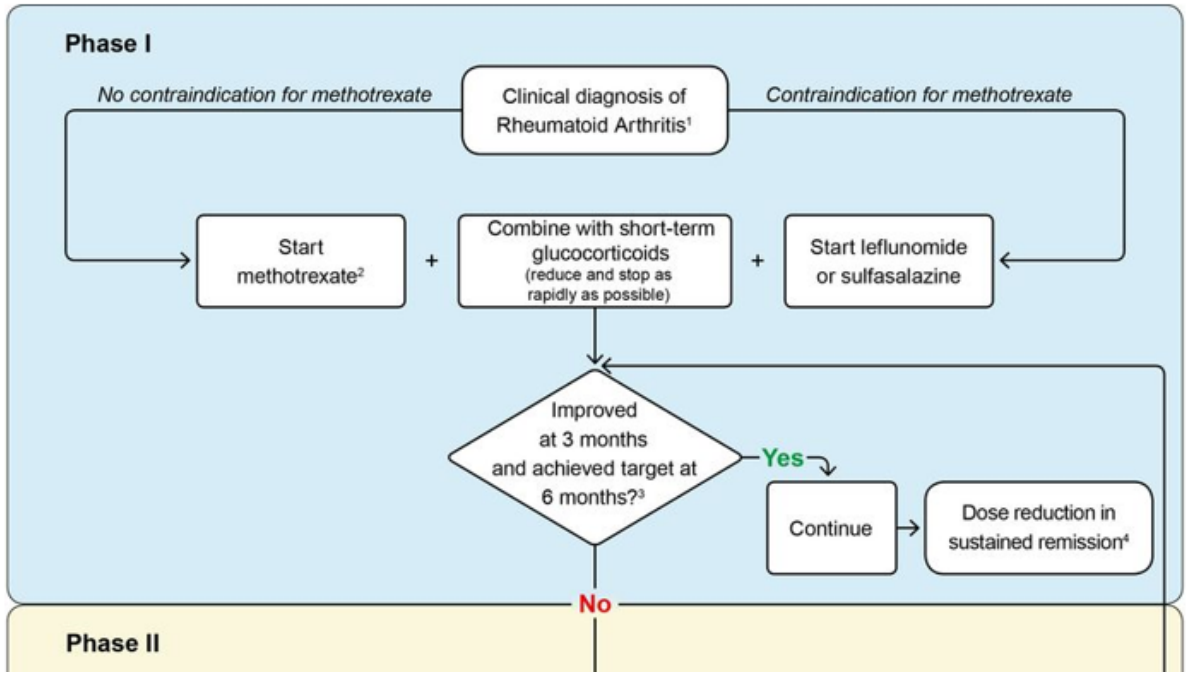
Common genetic variants do not impact clinical prediction of methotrexate treatment outcomes in early rheumatoid arthritis

Anton Öberg Sysojev [1,✉], Bénédicte Delcoigne [1], Thomas Frisell [1], Lars Alfredsson [2], Lars Klareskog [3,4]; The SRQ biobank group, Saedis Saevarsdottir [1,5], Magnus Boman [1,6], Leonid Padyukov [3,4], Johan Askling [1,7], Helga Westerlind [1]

PMCID: PMC12087826 PMID: 40190030

Why persistence?

- Indicates both tolerability and efficacy
- Avoids problem with missing clinical data -> bigger sample sizes!



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Project 1: prediction with machine learning (ML)

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ML: Aim

- Investigate if prediction accuracy of who stays on MTX treatment will increase if we use
  A. increasingly more detailed data
  B. more complex, data driven methods

ML: Materials

- Swedish Rheumatology Quality register (SRQ)
- Early RA diagnosed 2006-2014
- Starting MTX DMARD monotherapy
- Followed during the first year after diagnosis

ML: Methods

- Four data sets with different combinations of variables

- In all four data sets, the following variables were included:
  - → Sociodemographics
  - → Clinical data at RA diagnosis
  - → Medical history
  - → Drug history

- ICD and ATC codes included as
  I. Predefined diseases
  II. Chapters, blocks, categories and codes (ICD) and 1,3,5 and all digits (ATC)

Covariate data sets

	A	B	C	D
Demographics	X	X	X	X
A priori defined covariates	X			
All ICD codes up to 10 years before		X		
ICD Codes in time intervals			X	X
Contributory ICD codes in time intervals				X
ATC codes up to 5 years before		X		
ATC codes in time intervalls			X	X

ICD time intervals

0 - 1 year

1 - 5 years

5 – <10 years

ATC time intervals

0 -1 year

1 - 5 years

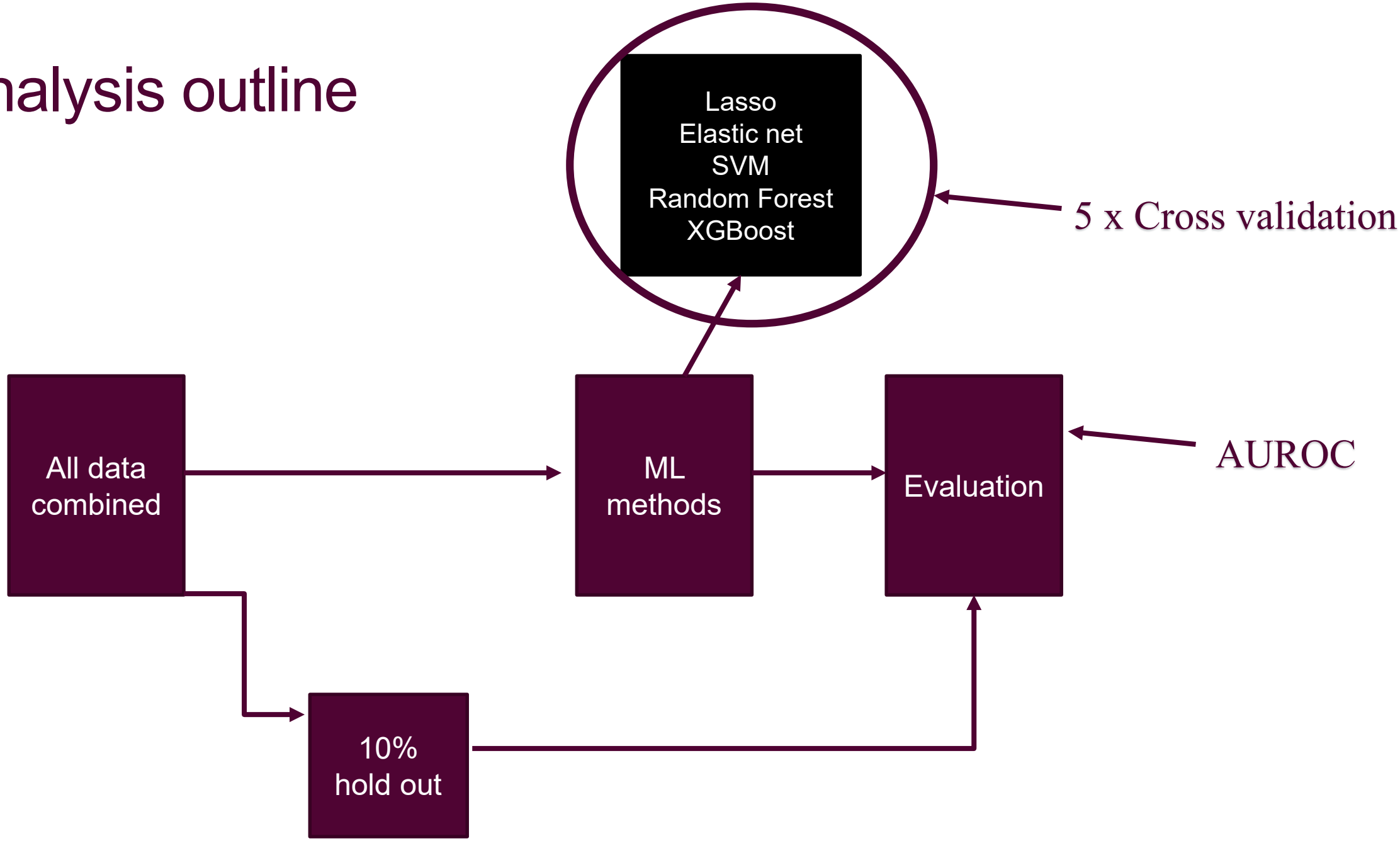
Covariates with frequency >= 0.5% included

ML: Methods

- Classical model building
  → Researcher

- Machine learning approach
  → Computer learns model from data

Analysis outline



ML: Results

	Overall
N	5475
Persistent at one year (%)	3834 (70)
Median age (IQR)	61 (20)
N women (%)	3737 (68)
Median year of diagnosis (IQR)	2010 (4)

ML: Results

- Sex and age: 0.58
- Epidemiologist: 0.66

- ML?

Covariate data set	A	B	C	D
N covariates	48	1313	2033	4126
Lasso regression	0.67	0.67	0.67	0.66
Elastic Net	0.67	0.67	0.67	0.66
Random Forest	0.62	0.61	0.63	0.61
SVM	0.65	0.58	0.58	0.53
XGBoost	0.61	0.64	0.63	0.63

Ensemble models – outline

- Different models might pick up different predictors
- By combining them we might increase prediction accuracy
- Or not…

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N covariates	48	1313	2033	4126
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XGBoost	0.61	0.64	0.63	0.63
Ensemble	0.63	0.65	0.65	0.65

ML: Conclusion

- All models improve from baseline model with just age + sex
- Clinical variables at baseline seems most important
- Our machine learning models performed (at least) as good as other treatment response predictions in RA

ML: Conclusions

- So medical history and “big data” might not be enough for our prediction
- What about genetic data? Could it contribute?

ML 2: ML with addition of genetic data

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Common genetic variants do not impact clinical prediction of methotrexate treatment outcomes in early rheumatoid arthritis

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Data types

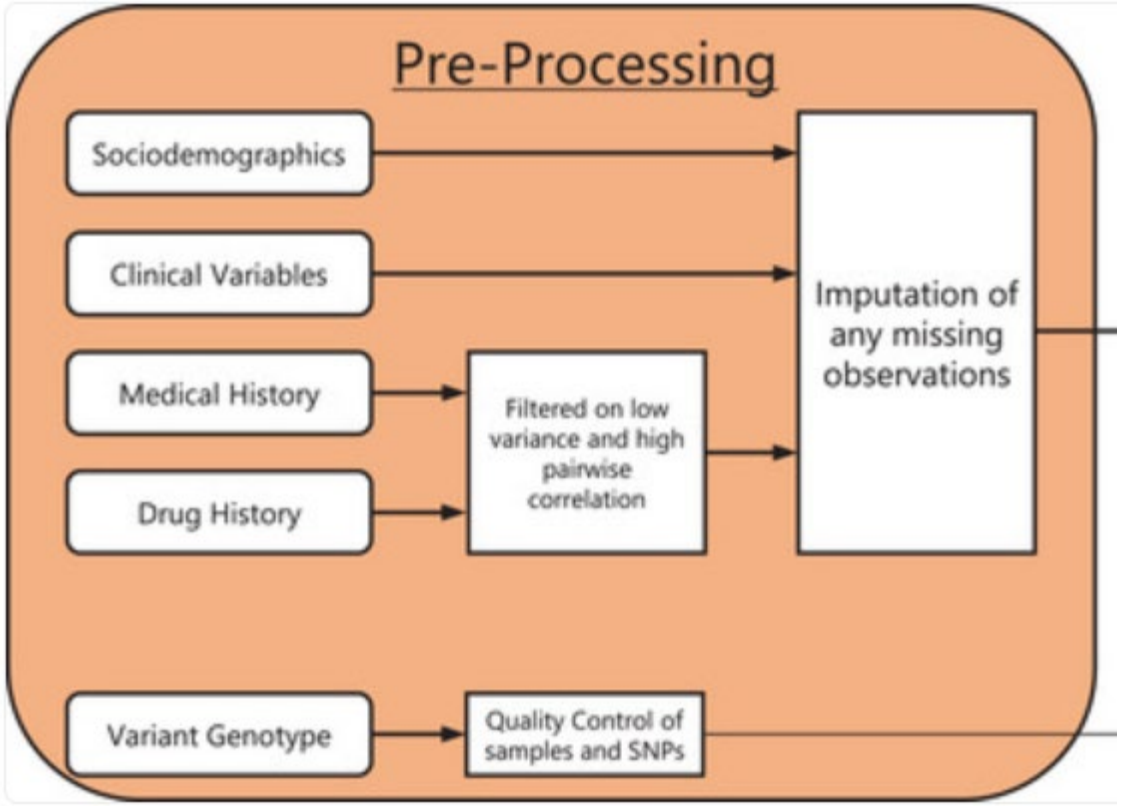
- Sociodemographics
- Clinical data at RA diagnosis
- Medical history
- Drug history

- Genotypic data

Genotypic data

- Polygenic risk scores
  - → Genetic liability towards a trait
- Principal components
  - → Composite of the entire genome
- Independent genetic markers
  - → Single markers could still be imporant
    - (Although unlikely)

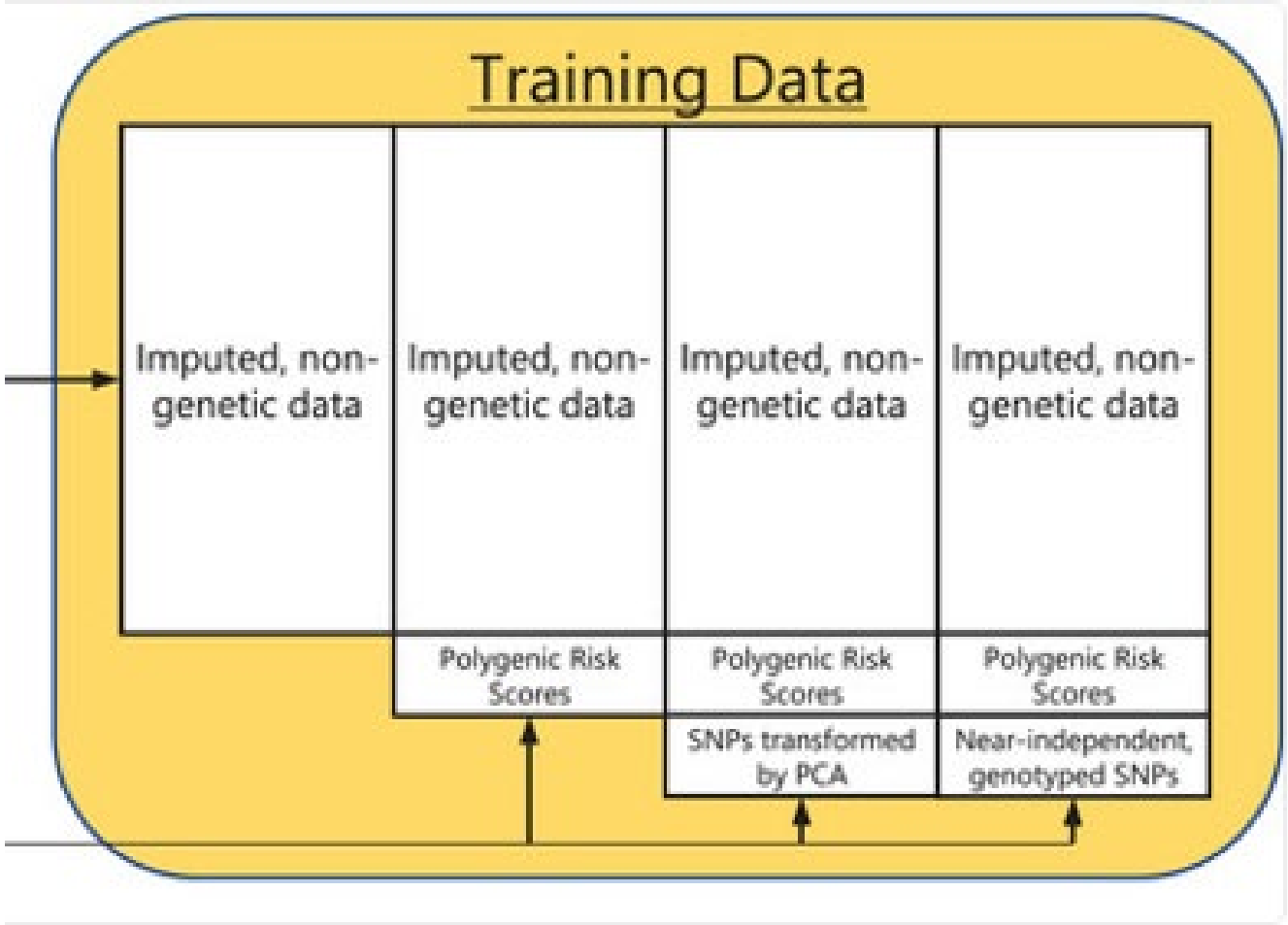
Pre-processing



Imputation w R-package ”missforest” (random forest-approach)

Sysojev et al, J Intern Medicine, 2025

Data processing



Sysojev et al, J Intern Medicine, 2025

Results demographics

- N = 2387 early RA
- Persistent = 67%

Variable type	N
Demographics, health care, medications, etc	105
Polygenic risk scores	17
Principal components	6
Genetic markers (SNPs)	16,000

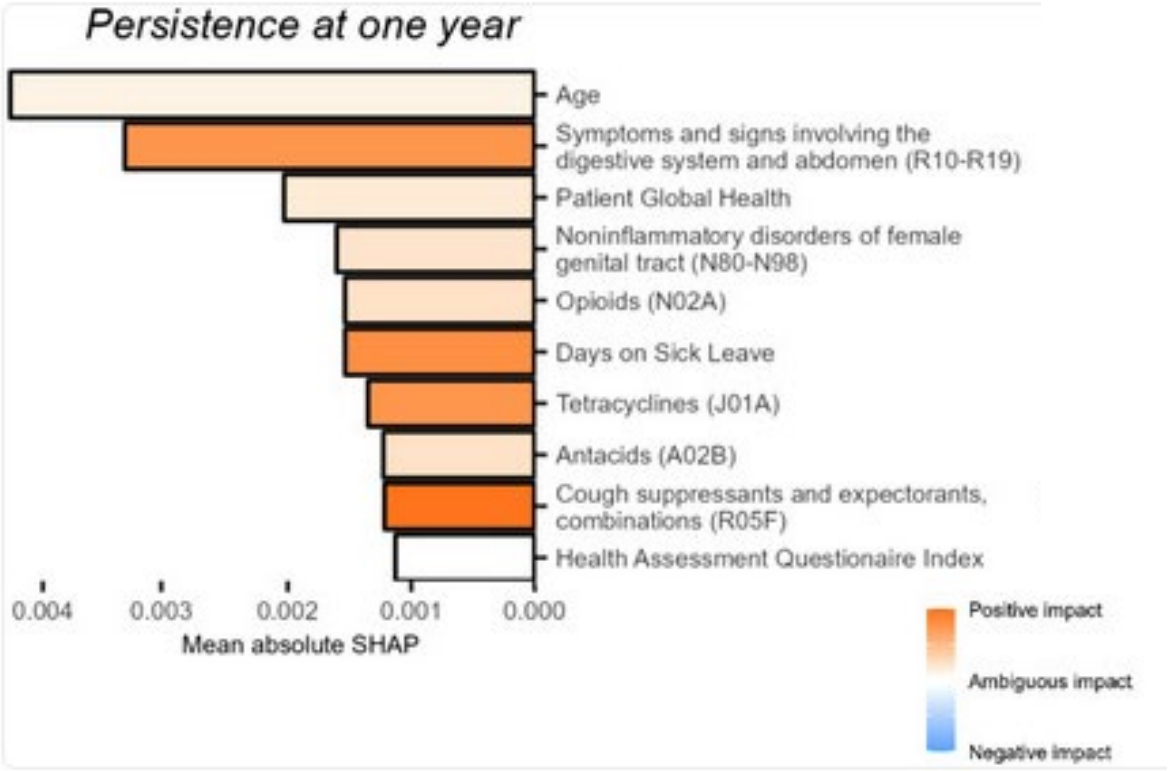
Prediction results AUC

ML model	Non-genetic data	Non-genetic data +PRS	Non-genetic data +PRS+PCA	Non-genetic data +PRS+SNPs
Logistic regression	0.60	0.60	0.59	-
Elastic net	0.62	0.62	0.62	0.60
Random forest	0.61	0.62	0.62	0.63
XGBoost	0.62	0.62	0.62	0.54

Is a AUCROC of 0.62-0.67 clinically useful?

Is it a ”good” result?

What features (variables) were important?



Sysojev et al, J Intern Medicine, 2025

But what about other prediction studies?

Study	Sample size	Model	Results
Lim et al. (2022a)	349 patients	Logistic Regression and Boosted Trees	AUC = 0.91, with hold-out validation AUC = 0.83
Myasoedova et al. (2022)	643 patients	Random Forest	AUC = 0.83, with hold-out validation AUC = 0.82

But what about other prediction studies?

Study	Sample size	Model	Results	Our validation
Lim et al. (2022a)	349 patients	Logistic Regression and Boosted Trees	AUC = 0.91, with hold-out validation AUC = 0.83	AUC = 0.52 (95% 0.47-0.58)
Myasoedova et al. (2022)	643 patients	Random Forest	AUC = 0.83, with hold-out validation AUC = 0.82	AUC = 0.63 (95% CI 0.57-0.68)

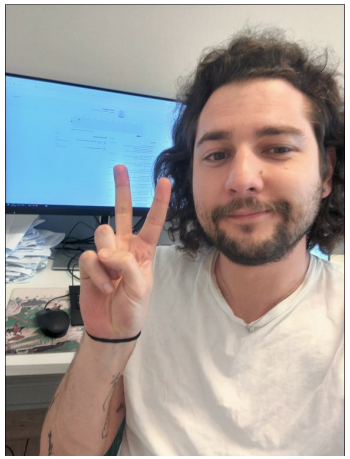
Persistence – conclusions

- Prediction of treatment response in RA is difficult!
- Not enough/right information in the data?
- Common genetic variance did not improve prediction
  → but we can't exclude it's still of importance…

Future work

- More data?
- More preprocessing of data?
- More advanced methods? AI? Neural networks…?

Acknowledgements



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Reumatiker förbundet

All patients, rheumatologists and nurses contributing data

Patient partners providing input

SRQ

SRQ biobank

Eira

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