

A Molecular Treatment Response Signature Improves Efficacy of T-Cell Therapy in Rheumatoid Arthritis

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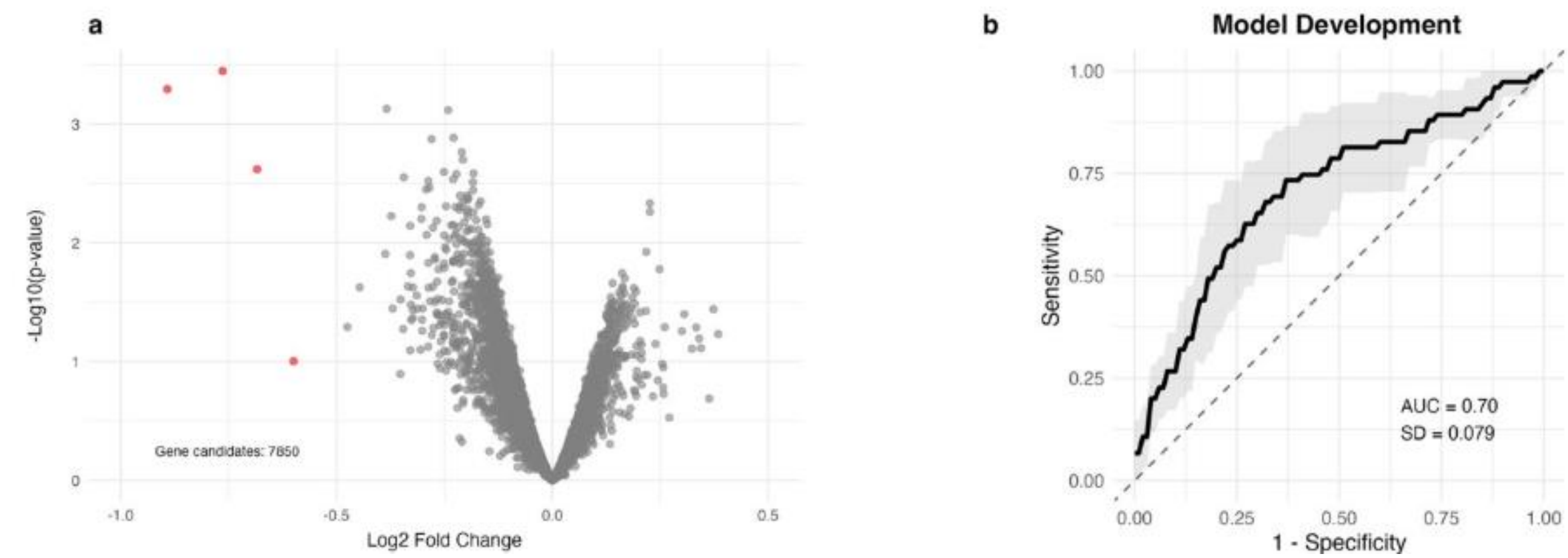
BACKGROUND

Rheumatoid arthritis (RA) exhibits marked clinical and biological heterogeneity, contributing to substantial variability in treatment response. This diversity limits the effectiveness of T-cell-modulating therapy, including abatacept, because underlying immune dysregulation and T-cell–associated pathways differ across individuals. In the absence of reliable predictive biomarkers, therapeutic decision-making remains largely dependent on trial-and-error approaches. To advance precision medicine in RA, we developed and validated a biologically informed molecular treatment response signature (MTRS) tailored to T-cell activation inhibition. The classifier was designed to identify patients more likely to respond to abatacept and to reduce use in those with a low likelihood of benefit.

METHODS

Blood-based multi-omics data, including transcriptomic profiles, SNP genotyping, baseline clinical characteristics, and treatment outcomes, were collected from multiple independent RA studies: a retrospective RA registry cohort, retrospective cohorts from company-sponsored clinical trials, and the prospective PREDICT clinical trial (NCT06390709). Candidate transcriptomic and genetic predictors were screened and reduced using a structured feature-selection strategy. Selected multi-omic features and baseline clinical parameters were used to develop a supervised machine-learning classifier trained to predict ACR50 response at 24 weeks with abatacept. Performance was evaluated by cross-validation in the training cohort and confirmed in two independent validation cohorts, including PREDICT.

Figure 1. Model development and Cross-validation



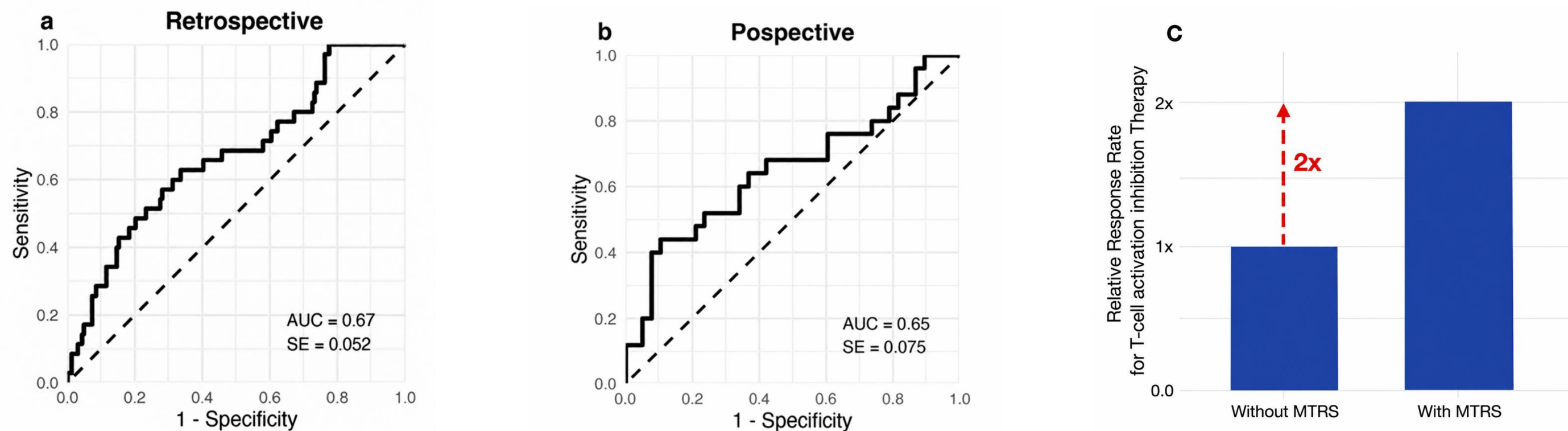
1a. Volcano plot of biologically relevant results from the training cohort: fold change (log2) and raw p-value between non-responders (NR) and responders (R) across 7,850 gene candidates. **1b.** Averaged ROC curves from cross-validation in the training cohort; mean AUC 0.70 (SD 0.079)..

Table 1. Baseline clinical characteristics

Variable	Category	Training	Retrospective Validation	Prospective Validation	P-value (Retro vs Pros)
N		360	199	63	
Age, mean (SD)		58.88 (12.50)	59.57 (13.29)	60.19 (14.57)	0.763
Gender, n (%)	Female	295 (81.9)	167 (83.9)	54 (85.7)	0.844
	Male	65 (18.1)	32 (16.1)	9 (14.3)	
Race, n (%)	White	312 (86.7)	170 (85.4)	52 (82.5)	0.340
	Asian	5 (1.4)	4 (2.0)	1 (1.6)	
	Black or African American	25 (6.9)	14 (7.0)	6 (9.5)	
	Native Hawaiian or Other Pacific Islander	0 (0.0)	1 (0.5)	0 (0.0)	
	Other	16 (4.4)	6 (3.0)	0 (0.0)	
	Unknown	2 (0.6)	4 (2.0)	4 (6.3)	
BMI, mean (SD)		30.49 (6.92)	30.95 (8.27)	30.10 (5.53)	0.354
ACPA*, n (%)	Negative	138 (39.5)	113 (56.8)	28 (44.4)	0.110
	Positive	211 (60.5)	86 (43.2)	35 (55.6)	
CRP, mean (SD)		7.91 (11.23)	12.25 (20.40)	9.20 (9.53)	0.109
CDAI, mean (SD)		28.48 (11.86)	31.02 (13.88)	29.47 (10.74)	0.354
Tender joint count, mean (SD)		10.72 (7.01)	11.88 (8.28)	10.11 (5.73)	0.059
Swollen joint count, mean (SD)		7.43 (5.06)	7.20 (5.86)	7.17 (4.69)	0.976
Patient global assessment, mean (SD)		54.57 (23.93)	64.98 (20.44)	57.30 (26.79)	0.040
Physician global assessment, mean (SD)		48.72 (19.44)	55.55 (21.43)	64.52 (18.24)	0.001
Patient pain, mean (SD)		55.24 (25.56)	63.26 (24.99)	57.22 (26.27)	0.111
Biologic naive, n (%)		70 (19.4)	85 (42.7)	28 (44.4)	0.884

*ACPA, anti-citrullinated protein antibodies.

Figure 2. Clinical validations and Relative response rate improvement

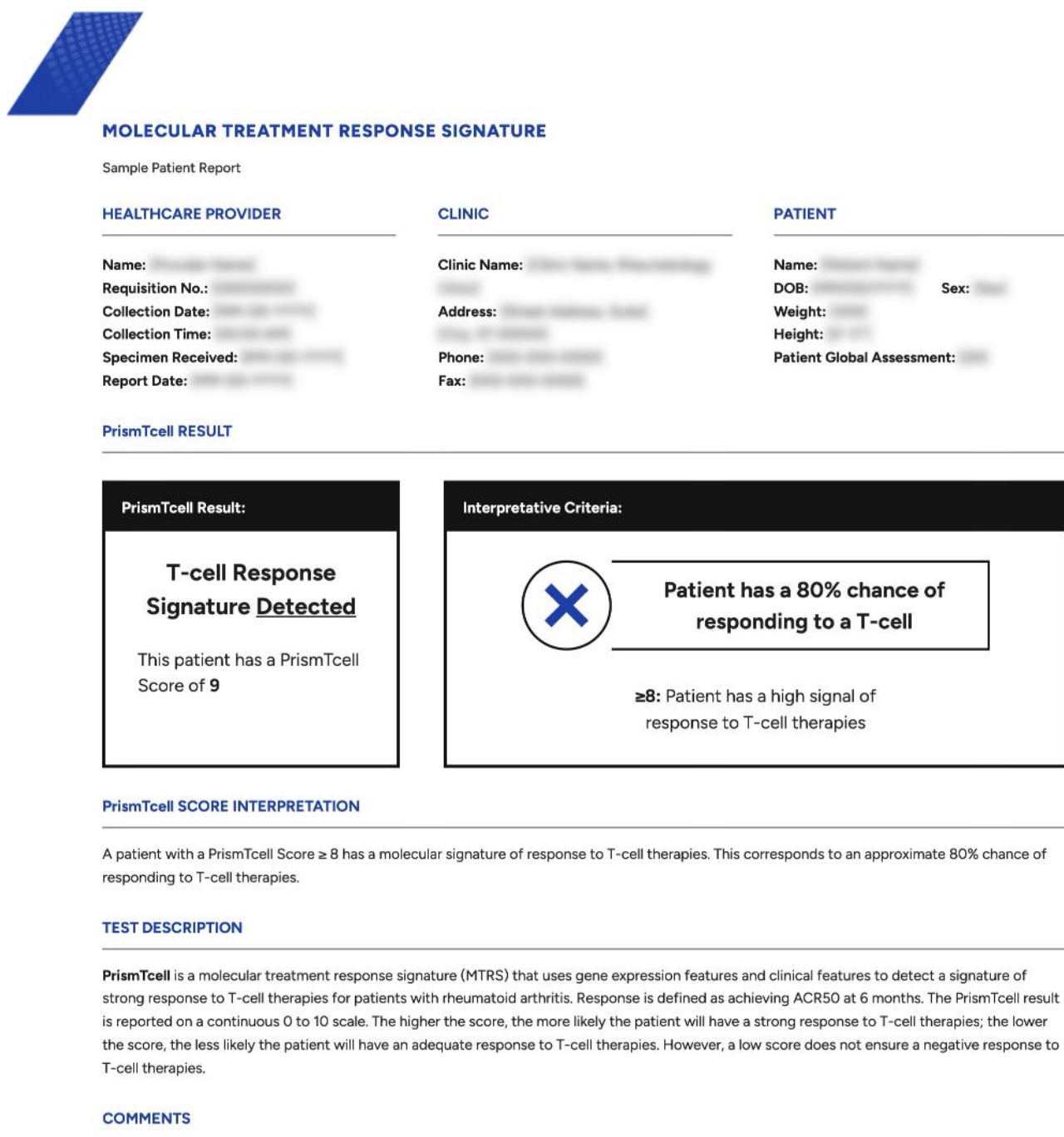


2a–b. ROC performance in the retrospective and prospective validation cohorts, AUC 0.67 (SE 0.052) and 0.65 (SE 0.075), respectively. **2c.** Relative change in T-cell therapy response rate without and with MTRS testing in RA patients.

RESULTS

Retrospective data were divided into training (n=360) and validation (n=199) cohorts. An additional 63 eligible patients from PREDICT were included for prospective clinical validation. Baseline characteristics were broadly similar across cohorts (**Table 1**). Transcriptomic profiling quantified 7,850 gene-expression features. Differential expression between responders and non-responders was visualized by volcano plot analysis using thresholds of absolute log2 fold change ≥ 0.5 and raw p-value ≤ 0.1 (**Fig 1a**). A selected set of multi-omic features, combined with baseline clinical parameters, was incorporated into the MTRS.

The MTRS showed consistent predictive performance. In cross-validation within the development cohort, the classifier achieved an AUC of 0.70 (SD 0.079) for distinguishing ACR50 responders from non-responders. In the two independent validation cohorts, AUCs were 0.67 (SE 0.052) and 0.65 (SE 0.075; **Fig 2a–2b**). Given the cutoff, the prospective cohort showed a 2-fold improvement in response rate among MTRS-selected patients (**Fig 2c**).



CONCLUSION

We developed and validated an abatacept-specific MTRS for patients with RA. The classifier provides patient stratification for T-cell activation inhibition, supports enrichment of clinical trial populations, and may enable more personalized treatment strategies aimed at improving therapeutic efficacy.