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COMMENTARY

Commentary on Cohen et al.: Role of Clinical Factors in Precision Medicine Test to Predict Nonresponse to TNFi Therapies in Rheumatoid Arthritis

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ABSTRACT

A 2021 study described the development and validation of a blood-based precision medicine test called the molecular signature response classifier (MSRC) that uses 23 features to identify rheumatoid arthritis (RA) patients who are likely nonresponders to tumor necrosis factor-α inhibitor (TNFi) therapy. Both the gene expression features and clinical components (sex, body mass index, patient global assessment, and anti-cyclic citrullinated protein) included in the MSRC were statistically significant contributors to MSRC results. In response to continued inquiries on this topic, we write this letter to provide additional insights into the contribution of clinical components to the MSRC on the Network-004 validation cohort.

Keywords: Clinical assessments; Rheumatoid arthritis; Molecular signature response classifier; Precision medicine

Key Summary Points

Despite the availability of multiple treatment options in rheumatoid arthritis (RA), predicting which patients will respond to any specific therapy remains a challenge.

The blood-based molecular signature response classifier (MSRC) identifies adult rheumatoid arthritis patients who are likely nonresponders to TNFi therapies so that they can be directed to a treatment with an alternative mechanism of action.

The MSRC assesses 23 features, including 19 gene expression features and clinical components [sex, body mass index (BMI), patient global assessment and anti-cyclic citrullinated protein (anti-CCP)].

The MSRC is a better predictor of TNFi nonresponse than any assessed singular clinical feature or combination of clinical features, thereby confirming the need for the genomic features to achieve classifier performance characteristics.

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MAIN COMMENTARY

In 2021, we published a study describing the development and validation of a blood-based precision medicine test that uses 23 features to identify rheumatoid arthritis (RA) patients who are likely nonresponders to tumor necrosis factor-α inhibitor (TNFi) therapy [1]. As part of the 2021 study, we evaluated the accuracy of predictions of likely TNFi nonresponders derived from a molecular signature response classifier (MSRC) to the ACR50 response outcome at 6 months. The MSRC was validated in biologic and targeted synthetic disease-modifying antirheumatic drug (b/ts DMARD)-naïve and TNFi-exposed patients. The primary outcome measure used to define response in clinical validation of the MSRC is ACR50; however, the MSRC predicts nonresponse according to additional validated outcome measures including ACR20, ACR70, Clinical Disease Activity Index (CDAI) low disease activity, CDAI remission, Disease Activity Score (DAS)28-C-reactive protein (CRP) low disease activity, and DAS28-CRP remission. The area under the receiver operating characteristic curve (AUC) for TNFi nonresponse prediction by the MSRC was 0.660 and 0.625 when results from a predictive model using only the 19 gene expression features were evaluated in an in-cohort cross-validation. Both the gene expression features and clinical components [sex, body mass index (BMI), patient global assessment, and anti-cyclic citrullinated protein (anti-CCP)] were statistically significant (Wald test, $p < 0.001$) contributors to MSRC results [1]. In response to continued inquiries on this topic, we write this letter to provide additional insights into the contribution of clinical components to the MSRC on the Network-004 external validation cohort.

Systematic literature reviews and meta-analyses of clinical studies continue to highlight the heterogeneity in RA and the need for new biomarkers predictive of therapeutic response beyond data available to clinicians when selecting a new RA therapy at the point of care [2–6]. Several biomarkers and clinical factors may be weakly predictive in groups of patients; yet singly or in combination these are not strong enough to guide treatment selection for individuals. For example, obese RA patients have lower clinical response rates to TNFi biologics [3, 7–9]. Male sex is associated with better response to TNFi therapy than female sex in early, but not established, RA [10–13]. Abnormally elevated levels of circulating anti-CCP is specific and sensitive for RA development and anti-CCP titer correlates with worse prognosis and erosions in RA patients overall [14, 15]. In an analysis of the AMPLE head-to-head trial, detection of high baseline anti-CCP2 antibody concentrations correlated with better responses to abatacept than adalimumab in biologic-naïve RA patients [16]. Results are conflicting between studies regarding the association of anti-CCP antibody levels and response to TNFi therapy [11, 17–28]. As other examples, current and past smokers may be less likely to achieve a good response to TNFi therapy [29–32], although contradictory analyses also have been reported [33]. Multivariate analyses considering clinical, serological, and genetic features also demonstrated an inverse association between smoking and adequate response to TNFi [29]. High baseline disease activity correlates with favorable TNFi responses [3]. Patient global assessment—included in the MSRC feature set—considers disease activity and complex underlying factors such as pain, depression, anxiety, and inability to participate in daily activities [34]. Numerous additional studies [35, 36], a review of which are beyond the scope of this letter, evaluated the likelihood of treatment success with TNFi in RA, yet a clinically useful model predicting TNFi therapeutic outcomes from routine clinical assessments alone has not been achieved.

In an exploratory analysis of the Network-004 study cohort [1], and based upon the AUC values, the MSRC was a better predictor of ACR50 nonresponse to TNFi than any singular clinical feature or combination of clinical features, as evaluated in a multivariate logistic regression model (Table 1), confirming the need for the genomic features to achieve classifier performance characteristics. Patients with a signature of nonresponse according to the MSRC were significantly more likely to inadequately respond to TNFi therapies than patients

Table 1 Prediction of ACR50 TNFi nonresponse in RA by MSRC or clinical features

	N	AUC	Odds ratio (95% CI)
b/ts DMARD-naïve			
MSRC	146	0.636	4.11 (2.02, 8.34)
BMI	146	0.513	1.54 (0.79, 2.98)
PtGA	146	0.596	2.03 (1.04, 3.96)
Male sex[a]	146	N/A	1.35 (0.60, 3.04)
Anti-CCP positive[b]	146	N/A	0.64 (0.33, 1.24)
BMI + PtGA + male + anti-CCP[c]	146	0.577	2.05 (1.05, 3.97)
TNFi-exposed			
MSRC	113	0.657	3.34 (1.50, 7.46)
BMI	113	0.452	1.09 (0.51, 2.33)
PtGA	113	0.627	2.57 (1.19, 5.54)
Male sex	113	N/A	1.24 (0.51, 3.04)
Anti-CCP	113	N/A	0.74 (0.35, 1.57)
BMI + PtGA + male + anti-CCP[c]	113	0.571	1.37 (0.53, 3.54)
Combined			
MSRC	259	0.640	3.06 (1.82, 5.14)
BMI	259	0.486	1.24 (0.75, 2.04)
PtGA	259	0.610	2.25 (1.36, 3.72)
Male sex	259	N/A	1.30 (0.72, 2.38)
Anti-CCP	259	N/A	0.68 (0.42, 1.12)
BMI + PtGA + male + anti-CCP[c]	259	0.568	1.92 (1.17, 3.16)

[a]Gender: male is coded as 1 and female is coded as 0
[b]Anti-CCP: positive is coded as 1 and negative is coded as 0
[c]Logistic regression model of the combination was optimized in the training data set; odds ratio for BMI, PtGA, male sex, and anti-CCP in the multivariate model are 1.05, 1.01, 0.43, and 0.42, respectively

lacking a signature (odds ratio 4.11, 3.34, and 3.89 in b/ts DMARD-naïve, TNFi-exposed, and the entire cohort, respectively). In this cohort, clinical features and their combination failed to compare with the MSRC statistical performance (Table 1). This indicates that the gene

expression features in the MSRC are important clinical evaluations to accurately predict TNFi nonresponse in RA patients.

In conclusion, and despite the availability of multiple treatment options in rheumatoid arthritis (RA), predicting which specific patients will respond to any RA therapy remains a challenge. While characteristics such as obesity, sex, smoking, and seropositivity for autoantibodies have been associated with response, or lack thereof, to some b/ts DMARDs [3, 37, 38]; clinical markers in isolation or aggregate have not been shown to be useful to predict future outcomes in RA with sufficient accuracy to guide individual treatment choices for individual RA patients initiating biologics or ts DMARDs.

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Data Availability. Data sharing is not applicable to this article as no datasets were generated or analyzed during the current study.

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