A Response to: Letter to the Editor Regarding A Molecular Signature Response Classifier to Predict Inadequate Response to Tumor Necrosis Factor-α Inhibitors: The NETWORK-004 Prospective Observational Study

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We wish to thank Dr. Holman, Dr. Keystone, Dr. Choy, Dr. Furst, Dr. Taylor, and Dr. Gaylis for their encouraging comments on our recent publication [1]. Our study combined machine learning and network biology to further refine our molecular signature response classifier (MSRC) test, which predicts non-response to tumor necrosis factor-alpha inhibitors (TNFi) in rheumatoid arthritis (RA). Subsequent analysis of the MSRC across two independent observational cohorts demonstrated its clinical validity, as described in our report.

An issue raised was that in our analysis, demographic characteristics did not differ significantly among patients who responded adequately to TNFi and those who did not. We understand this point. Our observation has been supported by post hoc analysis of the study, which showed that the MSRC evaluates and stratifies patients with respect to TNFi non-response regardless of anti-cyclic citrullinated peptide (CCP) antibody status (unpublished data) (Table 1). While the odds that a patient with an MSRC signature of TNFi non-response would fail to meet ACR50 response criteria at 6 months were approximately three times greater than among those who lacked the signal, we saw no significant difference in odds ratios between patients who were positive or negative for anti-CCP antibodies. This work is based on previously conducted studies and does not contain any new studies with human participants or animals performed by any of the authors.

We appreciate the authors' mention of the high-fidelity heart rate variability study [2], showing that autonomic nervous system (ANS) profiling can be a promising predictor of TNFi response in both RA and psoriatic arthritis. We agree that there exists an opportunity to explore various methods of vagus nerve stimulation (VNS) to promote immunosuppressive response, allowing targeted therapies such as TNFi to be more effective.

Indeed, we view MSRC and ANS/VNS as complementary and potentially synergetic tools within a multifactorial precision medicine approach to treating RA more effectively and rapidly. Precision medicine combines

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Table 1 No significant difference in odds ratios was observed between patients who were positive or negative for anti-CCP

	MSRC prediction of TNFi non-response at 6 months, per ACR50 criteria Odds ratio (95% confidence interval)
Anti-CCP positive ($n = 72$)	3.5 (1.3–9.7)
Anti-CCP negative ($n = 74$)	3.1 (1.2–8.3)

ACR50 American College of Rheumatology adequate response criteria of 50% improvement, *anti-CCP* anti-cyclic citrullinated peptide antibody, *MSRC* molecular signature response classifier

molecular, physiological, clinical, demographic, behavioral, environmental, and other variables to create tools that can improve the ability to predict and diagnose disease, as well as to estimate prognosis and treatment response [3].

In summary, we believe that our current findings, combined with previous work, show that the MSRC accurately predicts which patients with RA likely will not respond to TNFi therapy. We are optimistic about implementing MSRC clinically as a precision medicine approach to stratify patient groups to therapies most likely to be effective for them, with the goal of improving response earlier in the disease timeline, preventing progression, and reducing the substantial RA disease burden and cost. This article is based on previously conducted studies and does not contain any new studies with human participants or animals performed by any of the authors.

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Compliance with Ethics Guidelines. This article is based on previously conducted studies and does not contain any new studies with human participants or animals performed by any of the authors.

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