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

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INTRODUCTION

Background

- Rheumatoid arthritis (RA) is a systemic autoimmune disease characterized by chronic, symmetrical articular inflammation, pain, and disability
- About 90% of patients with RA are prescribed tumor necrosis factor-α inhibitor (TNFi) therapy after failing conventional synthetic disease-modifying antirheumatic drugs (DMARD), but the majority of patients fail to achieve a clinically meaningful change
- Matching each patient with RA to the right targeted therapy to reach the ACR-recommended treat-to-target goals of low disease activity or remission is an unmet medical need

PrismRA® Test Description

- A blood-based molecular signature response classifier integrating next-generation RNA sequencing data with clinical and laboratory features predicts the likelihood that a patient with rheumatoid arthritis will have an inadequate response to TNFi therapy
- 23 biomarkers in PrismRA:

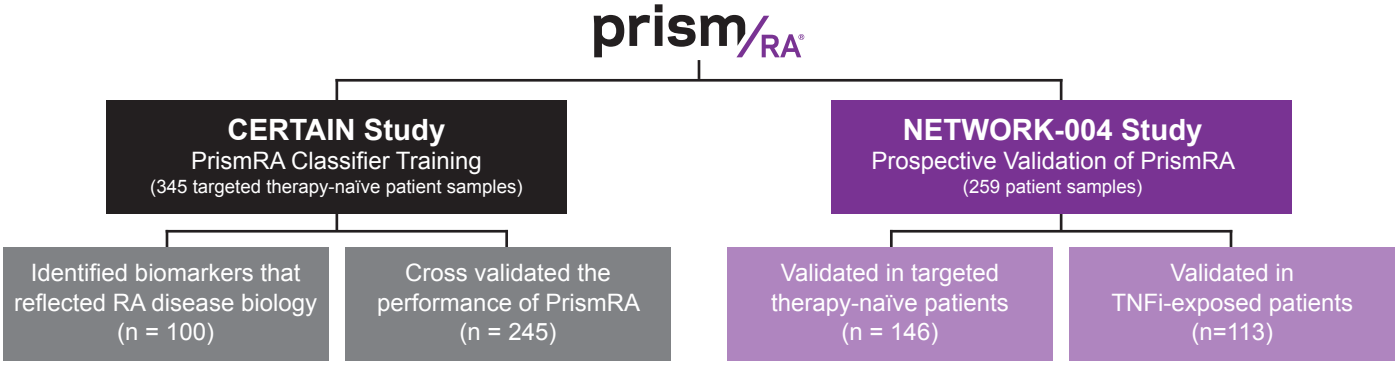
ALPL	COMMD5	KLHDC3	SPON2	Sex
ATRAID	GOLGA1	LIMK2	STOML2	Patient Global Assessment
BCL6	IL1B	NOD2	TRIM25	
CDK11A	IMPDH2	NOTCH1	ZFP36	Anti-CCP
CFLAR	JAK3	SPINT2	BMI	

Methods

- PrismRA was validated in blood samples from both the CERTAIN* and NETWORK-004 cohorts
- NETWORK-004 was a multicenter, blinded, prospective observational clinical study that included patients ≥18 years of age with active RA (CDAI >10, swollen joint count ≥4) who were targeted therapy-naïve receiving stable doses of methotrexate (15mg/week) for at least 10 weeks prior to baseline
- The primary endpoint evaluated the ability of PrismRA to identify patients who did not respond to TNFi therapy at 6 months according to ACR50
- Clinical assessments were collected at baseline, 3-month, and 6-month visits
- Molecular testing was conducted at baseline and at 3 months to identify patients unlikely to respond to TNFi therapy
- After baseline molecular testing, all patients initiated TNFi therapies, but dosage and TNFi selection were at the discretion of the provider
- Additional endpoints evaluated the prediction of inadequate response to TNFi at 3 and 6 months by ACR70, CDAI, and DAS28-CRP

*CORRONA (now CorEvitas) CERTAIN study: a comparative effectiveness study of biologic agents for rheumatoid arthritis patients

CLINICAL VALIDATION COHORTS



RESULTS

Odds of Not Responding to TNFi Therapy with a Prediction of Inadequate Response

Validated outcome measure	Odds ratio (95% CI; p-value) Targeted therapy-naïve (n=146)	Odds ratio (95% CI; p-value) TNFi-exposed (n=113)
ACR50, 6 months	**4.1** (2.0–8.3; 0.0001)	**3.3** (1.5–7.4; 0.0038)
ACR70, 6 months	**6.7** (2.7–16.7; <0.0001)	**6.0** (2.0–17.7; 0.0007)
CDAI LDA, 6 months	**3.6** (1.8–7.2; 0.0002)	**5.5** (2.4–12.4; <0.0001)
CDAI remission, 6 months	**8.8** (2.9–27.3; <0.0001)	**26.6** (3.4–209.8; <0.0001)
DAS28-CRP LDA, 6 months	**3.6** (1.8–7.3; 0.0003)	**6.7** (2.8–16.1; <0.0001)
DAS28-CRP remission, 6 months	**5.8** (2.6–13.0; <0.0001)	**2.1** (0.9–5.0; 0.0878)
% of patients predicted to not respond	**44.5%**	**40.7%**

ACR = American College of Rheumatology, CDAI = clinical disease activity index, LDA = low disease activity, DAS28-CRP = disease activity score 28-joint count with C-Reactive protein

- 32.4% (22/68) of patients without a molecular signature of inadequate response achieved CDAI remission at 6 months in response to TNFi therapy, while only 5.1% (4/78) of those with a molecular signature achieved remission
- Among patients initiating their first targeted therapy, those with a molecular signature of inadequate response were 3 to 9 times more likely to not respond to a TNFi therapy
- Patients with a molecular signature of inadequate response were as much as 27 times less likely to achieve CDAI remission at 6 months than patients lacking the molecular signature
- The molecular signature was predictive of inadequate response to TNFi therapy according to multiple clinically validated measures including ACR50, ACR70, CDAI, and DAS28-CRP

CONCLUSION

- Validation of PrismRA involved two independent studies and patient populations, reproducing for the first time the predictive ability of molecular biomarkers using RA biology
- Among both targeted therapy-naïve and TNFi-exposed patients, patients with a molecular signature of inadequate response are unlikely to respond to TNFi therapy at 3 or 6 months as assessed by ACR50, ACR70, CDAI, and DAS28-CRP
- When providers use PrismRA test results to stratify patients to treatment, patients with a molecular signature of inadequate response to TNFi therapies can be directed to a therapy with an alternative mechanism of action to avoid unnecessary expenses and potential toxicities
- Although PrismRA is not intended to be interpreted as a likely positive response to TNFi therapies, those who lack this signature can proceed with TNFi therapy and possibly achieve an increased response rate relative to the unstratified population
- Access to precision medicine at multiple points during the treatment of patients with RA expands and complements the clinical information available to providers, thereby providing patient-specific data to improve care and shorten the time necessary to achieve treatment goals

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