Anthem

Medical Policy

Subject: Molecular Signature Test for Predicting Response to Tumor Necrosis Factor Inhibitor Therapy
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Description/Scope

This document addresses molecular signature testing (PrismRA, Scipher Medicine, Waltham, MA) to predict response to Tumor Necrosis Factor inhibitor (TNFi) therapy. The molecular signature test includes RNA sequencing and gene expression data to determine if an individual is unlikely to respond to TNFi therapy.

Position Statement

Investigational and Not Medically Necessary:

Molecular signature testing to predict response to Tumor Necrosis Factor inhibitor (TNFi) therapy is considered**investigational and not medically necessary** for all uses, including but not limited to guiding treatment for rheumatoid arthritis.

Rationale

The use of signature molecular testing has been investigated for predicting response to TNFi therapy using RNA sequencing and gene expression data. The available literature addresses a single test, the PrismRA, developed to assist providers in therapy selection by identifying individuals that are predicted to be unlikely to respond to TNFi therapy.

In 2020, Mellors and colleagues reported the results of a cross-platform, cross-cohort study to develop a classification algorithm to predict whether individuals diagnosed with rheumatoid arthritis (RA) will respond to anti-TNF drug treatment. The authors of the study analyzed gene expression biomarkers for 376 subjects who had participated in another trial of TNFi effectiveness (the CERTAIN trial by the Consortium of Rheumatology Researchers of North America [CORRONA]; Pappas, 2014). Serum samples had been collected prior to longitudinal evaluations over at least 6 months of follow-up while being treated with a TNFi (adalimumab, certolizumab pegol, etanercept, golimumab, or infliximab). Response to treatment was measured as the percentage of subjects who experienced at least a 50% reduction in symptom severity at 6 months as measured by the American College of Rheumatology (ACR) core set of RA markers (ACR50 score). The authors of this study noted that only 30.2% of individuals saw this level of benefit from TNFi treatment. In other words, 30.2% were responders and 69.8% were nonresponders. The authors also note that this response rate is similar to that seen in other studies (Alonso-Ruiz, 2008).

Mellors and colleagues described a study involving the analysis of serum biomarkers from 58 subjects as a discovery cohort 143 subjects as a training cohort and 175 subjects used as a validation cohort. For the discovery cohort, they evaluated the biomarker profiles of 58 anti-TNFi treatment-naïve individuals. Mann-Whitney U tests were used to eliminate biomarkers that were not statistically different between responders and non-responders. Further statistical analysis identified 70 biomarker features that were most different between responders and non-responders. These features included gene expression products, single-nucleotide polymorphisms (SNPs), and clinical factors. All members of the discovery cohort were female, but the relationship of this 70-feature set to response/non-response was validated for the entire training set including males and females.

As a second step, the authors iteratively analyzed their candidate biomarker set in samples from the 143-subject training set. They created a Random Forest model using the 25 features most associated with non-response. They next evaluated the ability of this model to predict response to therapy for the 175 individuals in the validation cohort. None of the validation subjects had been included in the discovery or training sets.

Mellors: Results of Testing in Validation Cohort

	Nonresponse	Responder	
Nonresponse Predicted	61	7	68
Response Predicted	61	46	107
	122	53	175

Positive and negative predictive value based on pre-test likelihood of nonresponse = 69.8%:

Sensitivity	50.0% (95% CI 40.8-59.2%)
Specificity	86.8% (95% CI 74.7-94.5%)
Positive likelihood ratio	3.79 (1.86 – 7.72)
Negative Likelihood ratio	0.58 (0.47 – 0.71)
Positive Predictive Value	89.74% (81.1% to 94.7%)
Negative Predictive Value	42.9% (37.93% to 48.0%)

Of those who responded to treatment, 86.8% (46/53) had a test result indicating that they were likely to respond. Half of the subjects in the validation set who did not respond to treatment had a test that indicated they were likely to respond. Among subjects with a test indicating nonresponse, the ratio of nonresponders to responders was 3.79. For those with tests indicating response, the ratio of nonresponders to responders was 0.58. This indicates that individuals with a positive test are 6.3 (3.79/0.58) times as likely to be nonresponders as they are to be responders.

This study has several limitations. Although the authors showed correlation with non-response for this small set of subjects, this study does not show that use of this model can prospectively improve response rates among individuals with RA proposed for TNFi treatment. SNP alleles may vary among ethnic groups and the training and validation cohorts were predominately Caucasian (88.1% and 84.6%, respectively). The authors report no significant difference in the panel's ability to predict response among individuals of other ethnicities. Additional work is needed to prospectively evaluate prediction performance in diverse populations.

In 2021, Cohen and colleagues published the results of a prospective observational study of a molecular signature response classifier (MSRC) using 23 features (PrismRA) to predict inadequate response to TNFi treatment. A total of 146 individuals completed the 24-week study with clinical assessments occurring at baseline, 3 months, and 6 months. Assessments included patient global assessment of pain, patient global assessment of disease activity, Clinical Disease Activity Index (CDAI) score, Health Assessment Questionnaire, and C-reactive protein (CRP). The 3-month visit also included molecular and clinical data such as the ACR50, ACR70,

CDAI, and the Disease Activity Score-28 with CRP (DAS28-CRP) that was then used to predict response to TNFi therapy. PAXgene RNA samples were collected at all 3 visits. The MSRC detected non-response in 46/113 (40.7%) TNFi-exposed individuals and the difference in model scores was observed between individuals that did have an MSRC of non-response and did not have an MSRC of non-response ($p<0.05$). These results correspond to odds ratio (OR) of 3.3-26.6 for individuals with the molecular signature having a non-response to TNFi therapy according to all the criteria except for DAS28-CRP. Of the 146 individuals, 26/146 (17.8%) achieved CDAI remission at the 6-month visit. A total of 22/68 (32.4%) of individuals that did not have a molecular signature for non-response achieved remission and 4/78 (5.1%) for those with the molecular signature for non-response achieved remission. The limitations include lack of inclusion of development of antidrug antibodies which may impact treatment response, and the MSRC results were not used to inform treatment selection. Also, some of the outcome measures were subjective assessments which may have an impact on the individual's outcome in relation to MSRC accuracy estimation.

Jones (2021) reported the results of a retrospective study involving residual samples from 174 subjects with RA who had participated in the NETWORK-004 study. A total of 100 subjects were TNFi treatment naïve and 74 had received prior treatment with TNFi therapy. The majority of subjects had received concomitant methotrexate therapy (> 80%) and treatment with all five available TNFi drugs were represented in the study population. Based on ACR50 measurements at 6 months, the authors reported a positive predictive value (PPV) of 87.7% (95% confidence interval [CI]: 78–94%), sensitivity of 60.2% (95% CI: 50–69%), and specificity of 77.3% (95% CI: 65–87%).

Strand (2022a) described an interim analysis of data from the Study to Accelerate Information of Molecular Signatures (AIMS) in Rheumatoid Arthritis registry involving subjects with RA who underwent testing with the 21-factor PrismRA assay and who had test-result based treatment. The report included results from 85 subjects who completed 24 weeks of PrismRA-guided therapy. The primary endpoint was therapeutic responsiveness defined as ACR50 at 24 weeks. Subjects were stratified into 4 groups: 1) PrismRA results indicating non-responder status and who were treated with non-TNFi therapy; 2) PrismRA results indicating non-responder status and who were treated with TNFi drugs; 3) PrismRA results indicating responder status and treated with TNFi drugs; and 4) PrismRA results indicating responder status and treated with non-TNFi therapy. In subjects receiving therapy in alignment with PrismRA test results (Groups 1, 3 and 4), the 24-week mean ACR50 responses were reported to be 39.6%. In the groups where subjects had a PrismRA result indicating non-response and who treated with non-TNFi therapy, significantly improved therapeutic responses were reported (ACR50: Group 1 = 34.8% vs. Group 2 = 10.3%, $p=0.05$; ≥ MID [minimally important differences] in CDAI: Group 1 = 56.2% vs. Group 2 = 15.4%, $p=0.009$). No significant differences were observed between groups that underwent treatment with non-TNFi drugs but had differing PrismRA results (ACR50: Group 1 = 34.8% vs. Group 4 = 33.3%, $p>0.05$; ≥ MID in CDAI: Group 1 = 56.2% vs. Group 4 = 42.9%, $p>0.05$). Finally, subjects with PrismRA results indicating non-response had significantly lower therapeutic responses when treated with TNFi therapy compared with subjects with responder PrismRA status subjects (ACR50: Group 2 = 10.3% vs. Group 3 = 45.8%, $p=0.005$; ≥ MID in CDAI: Group 2 = 15.4% vs. Group 3 = 45.0%, $p=0.02$). These interim results are promising and the final results from this trial should provide additional useful data addressing the clinical utility of the PrismRA test.

Strand (2022b) published a second interim study using AIMS registry data. The report included data from 470 subjects with moderate to severe RA who had treatment decisions based on PrismRA results and had data at 12-week follow-up. Data from 274 subjects with 24-week data were also reported. The primary and secondary endpoints of the clinical outcomes analysis were changes from baseline in absolute CDAI scores at 24 weeks and 12 weeks. The authors reported that subjects with PrismRA non-responder status who received non-TNFi therapy experienced up to 1.8-fold greater improvement in CDAI scores when compared to subjects with non-responder status who received TNFi therapy (12 weeks: 12.2 vs. 8.0, $p=0.083$; 24 weeks: 14.2 vs. 7.8, $p=0.009$). Subjects with high baseline disease activity and PrismRA non-responder status had a 1.7-fold greater improvement in CDAI scores when treated with a non-TNFi therapy compared to PrismRA non-responder status subjects treated with TNFs (8.9 vs. 15.1, no p-value provided). This corresponded to 38.9% of subjects achieving a lower disease activity level in response to TNFi therapy compared to 55.7% with non-TNFi therapy, a 43.2% relative improvement. Subjects with moderate baseline disease activity had a 3.1-fold greater improvement (3.1 vs. 9.7, respectively, no p-value provided). A greater proportion of PrismRA non-responder status subjects experienced worsening CDAI scores when treated with TNFi therapy compared with non-TNFi therapy (high baseline disease activity: 27.8% vs. 17.1%, no p-value provided). Finally, compared to subjects with PrismRA responder status who received non-TNFi therapy, those receiving TNFi therapy had 1.6-fold greater improvement in CDAI scores at 12 weeks (8.0 vs. 10.2; $p=0.087$) and a 1.9-fold improvement at 24 weeks (7.8 vs. 12.7; $p=0.012$). As with the previously discussed Strand study, these interim results are promising and indicate potential clinical utility for the use of PrismRA test results in informing treatment decisions in individuals with RA. Full results from the completed study will provide a better picture of this issue.

In 2022, Curtis published a retrospective comparative cohort study using data from 627 subjects from the AIMS registry compared to 2721 propensity-match control subjects from electronic health records. A statistical matching method (PSM) was applied to allow comparison of the two groups, leading to a total of 489 PrismRA-guided treatment/experimental group subjects and 761 control group subjects being included in the final analysis. Thirty-eight experimental group subjects and 494 control group subjects switched biologic or targeted synthetic disease-modifying antirheumatic drugs (b/tsDMARDs) during the 6-month study course. The authors noted that the PrismRA group had higher baseline disease activity vs. the control group. In the PrismRA group 368 subjects (59%) were identified as having non-response signatures to TNFi and 441 (70%) were prescribed a b/tsDMARD that aligned with PrismRA result. After PSM, the odds of responding to b/tsDMARD therapy at 6 months were significantly greater in the PrismRA group vs. controls ($p<0.0001$). Changes in the response rates in PrismRA group were between 1.6 and 2.9 times greater than those in the control group, depending upon the measure used. In the PrismRA group the ability to detect a non-response signature was evaluated in TNFi treated subjects (n=369), with 54% who did not respond also having a TNFi non-response signature. Conversely, 88% of PrismRA group subjects with a non-response signature did not respond to TNFi therapy (ACR50: PPV=88%, sensitivity=54%, specificity=70%, area under the curve [AUC]=0.65). Finally, PrismRA group subjects predicted to be likely non-responders to TNFi therapy were approximately 3 times less likely to satisfy ACR50 criteria (OR 2.73) after 24 weeks of TNFi therapy. As with the prior studies, these results indicate that use of the PrismRA test can help identify the likelihood of drug response in individuals for whom TNFi therapy is recommended. However, these results do not demonstrate changes in health outcomes such as avoided complications, disease flareups, and morbidity.

The current version of the American College of Rheumatology (ACR) guideline for the treatment of rheumatoid arthritis does not address the use of molecular signature testing (Fraenkel, 2021).

Molecular signature testing offers the potential to improve treatment response by avoiding TNFi therapy when an individual is predicted to be a non-responder. Additional peer-reviewed published studies are warranted, including studies with diverse populations, validation of responders versus non-responders, and the ability of the test to contribute to the improvement of net health outcomes of individuals with RA. The ACR provides no guidance regarding molecular signature testing. The integration of this test within standardized endorsed treatment guidelines is needed to demonstrate clinical utility. Molecular signature testing is being considered for other indications, such as ulcerative colitis, Crohn's disease, among others, however there is no published literature for indications other than RA.

Background/Overview

RA is an autoimmune disease with no current cure or known underlying cause. Although arthritis is almost always present and is often the most troubling manifestation of the disorder, the disease is systemic and can have severe effect on other organs such as the eyes, lungs, heart, and integument.

“Classic” RA is characterized by pain, swelling, and stiffness in many joints. Small joints in the wrists, hands, and feet are typically involved early in the course of illness. Shoulders, elbows, knees, and ankles are often affected. Involvement of the jaw, spine, or hips is less common.

The symptoms of RA reflect an intense autoimmune inflammation. Symptoms commonly fluctuate over time with periods of little activity and “flare” periods with severe overt inflammation. Inflammation of the joints will lead to progressive disabling joint destruction in most untreated individuals. While symptoms may wax and wane, joint destruction can progress even in the absence of severe symptoms. Current guidelines recommend aggressive control of inflammation as soon as possible after the disease is recognized.

Generally effective disease-modifying antirheumatic drugs (DMARDs) include non-steroidal anti-inflammatory drugs, methotrexate, corticosteroids, leflunamide, sulfasalazine, and TNFs. Advanced immune suppression may also be achieved with janus kinase inhibitors, abatacept, or anti-interleuken 6 receptor antagonists. Each of these treatments can have severe adverse effects. Finding the best combination of treatments for each individual is often challenging. Care should be guided by an experienced practitioner with expert knowledge of RA and its treatment.

Therapy is typically guided by composite metrics incorporating objective findings (such as the number of inflamed or tender joints) and subjective measures (such as pain, fatigue, or stiffness). Reductions of 20%, 50%, or 70% in core metrics specified by ACR form the basis for the ACR20, ACR50, and ACR70 scores, respectively. The European League Against Rheumatism (EULAR) has a different metric called the Disease Activity Score Using 28 Joints (DAS28). ACR20, ACR50, ACR70, and DAS28 are commonly used as outcomes measures in clinical research. The Simplified Disease Activity Index (SDAI) and the Clinical Disease Activity Index (CDAI) tools can be used to guide therapy response in clinical practice.

The ACR 2021 RA treatment guideline strongly recommends initiating TNFi therapy when disease activity is moderate or high despite disease-modifying anti-rheumatic drugs (DMARDs), with the recommendation to alter therapy if needed due to comorbidities (Fraenkel, 2021). The TNFi therapies include adalimumab, certolizumab pegol, etanercept, golimumab, or infliximab.

The molecular signature test analyzes 23 biological features including SNPs derived from RNA sequencing, gene expression levels, serum peptides, and other disease-associated clinical features to identify a molecular signature of an individual that may or may not respond to TNFi therapy. The results of the test are sorted into categories (very high, high, moderate, no signal) that are purported to predict the likelihood of nonresponse to TNFi therapy.

Coding

The following codes for treatments and procedures applicable to this document are included below for informational purposes. Inclusion or exclusion of a procedure, diagnosis or device code(s) does not constitute or imply member coverage or provider reimbursement policy. Please refer to the member's contract benefits in effect at the time of service to determine coverage or non-coverage of these services as it applies to an individual member.

When services are Investigational and Not Medically Necessary:
When the code describes a procedure indicated in the Position Statement section as investigational and not medically necessary.

CPT

81479	Unlisted molecular pathology procedure [when specified as PrismRA test]
81599	Unlisted multianalyte assay with algorithmic analysis [when specified as PrismRA test]

ICD-10 Diagnosis

	All diagnoses

References

Peer Reviewed Publications:

1. Alonso-Ruiz A, Pijoan JI, Ansuategui E, et al. Tumor necrosis factor alpha drugs in rheumatoid arthritis: systematic review and meta analysis of efficacy and safety. BMC Musculoskelet Disord. 2008; 9:52.
2. Cohen S, Wells AF, Curtis JR, et al. A molecular signature response classifier to predict inadequate response to tumor necrosis factor-α inhibitors: the NETWORK-004 prospective observational study. Rheumatol Ther. 2021; 8(3):1159-1176.
3. Curtis JR, Strand V, Golombek S, et al. Patient outcomes improve when a molecular signature test guides treatment decision-making in rheumatoid arthritis. Expert Rev Mol Diagn. 2022 Nov 3:1-10.
4. Jones A, Rapisardo S, Zhang L, et al. Analytical and clinical validation of an RNA sequencing-based assay for quantitative, accurate evaluation of a molecular signature response classifier in rheumatoid arthritis. Expert Rev Mol Diagn. 2021; 21(11):1235-1243.
5. Mellors T, Withers JB, Ameli A, et al. Clinical validation of a blood-based predictive test for stratification of response to tumor necrosis factor inhibitor therapies in rheumatoid arthritis patients. Network and Systems Medicine. 2020; 3(1):1-14.
6. Pappas DA, Kremer JM, Reed G, et al. Design characteristics of the CORRONA CERTAIN study: a comparative effectiveness study of biologic agents for rheumatoid arthritis patients. BMC Musculoskelet Disord. 2014; 15:113.
7. Strand V, Cohen SB, Curtis JR, et al. Clinical utility of therapy selection informed by predicted nonresponse to tumor necrosis factor-α inhibitors: an analysis from the Study to Accelerate Information of Molecular Signatures (AIMS) in rheumatoid arthritis. Expert Rev Mol Diagn. 2022a; 22(1):101-109.
8. Strand V, Zhang L, Arnaud A, et al. Improvement in clinical disease activity index when treatment selection is informed by the tumor necrosis factor-α inhibitor molecular signature response classifier: analysis from the study to accelerate information of molecular signatures in rheumatoid arthritis. Expert Opin Biol Ther. 2022b; 22(6):801-807.

Government Agency, Medical Society, and Other Authoritative Publications:

1. Fraenkel L, Bathon JM, England BR, et al. 2021 American College of Rheumatology guideline for the treatment of rheumatoid arthritis. Arthritis Rheumatol. 2021; 73(7):1108-1123.

Index

PrismRA

The use of specific product names is illustrative only. It is not intended to be a recommendation of one product over another, and is not intended to represent a complete listing of all products available.

Document History

Status	Date	Action
Reviewed	08/10/2023	Medical Policy & Technology Assessment Committee (MPTAC) review. Revised Rationale and References sections.
Reviewed	08/11/2022	MPTAC review. Updated Description, Rationale and References sections.
New	08/12/2021	MPTAC review. Initial document development.

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