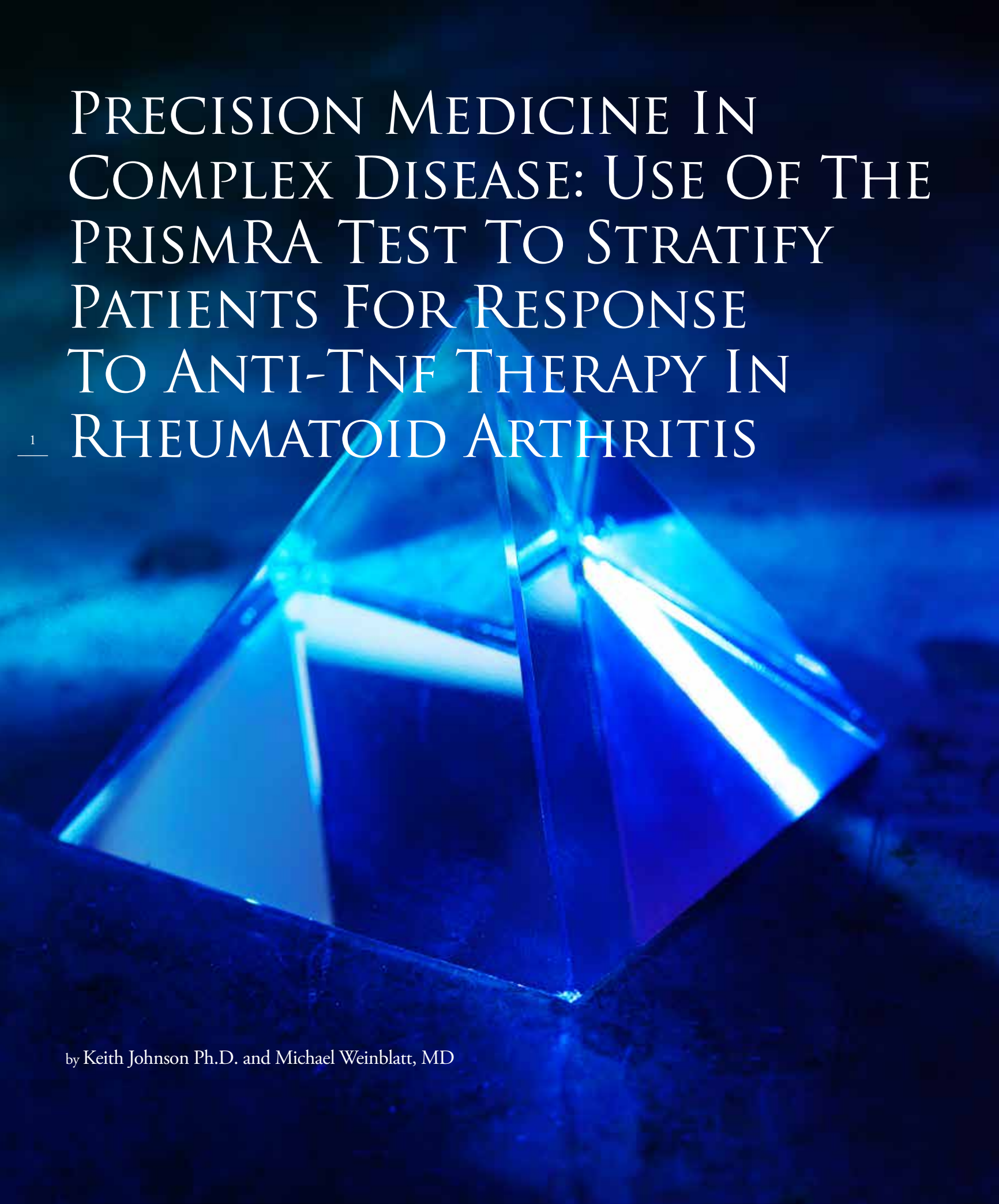
Precision Medicine In Complex Disease: Use Of The PrismRA Test To Stratify Patients For Response To Anti-Tnf Therapy In Rheumatoid Arthritis



by Keith Johnson Ph.D. and Michael Weinblatt, MD

Precision medicine approaches tailor a patient's therapy based on predicted response, often stemming from a genomic characterization of the disease. Precision medicine is becoming standard practice in oncology which can be characterized by genetic factors; a prime example is the approval and use of Herceptin only for women with Her2 positive breast tumors. However, examples of precision medicine remain elusive in complex diseases, which are characterized by genetic, genomic, and environmental factors, even though many therapies are indeed targeting a specific disease biology. The pursuit of precision medicine in complex disease has lagged behind in oncology due to the fact that determining the underlying disease biology in a patient with a complex disease has historically been difficult to ascertain.

Rheumatoid Arthritis (RA), a complex disease, affects approximately 1.3 million adults in the United States alone, costing the health care system and society over $60 billion in drugs, surgery, hospitalization, disability and sick days.[1-2] Common therapies to treat RA are Disease Modifying Anti-Rheumatic Drugs (DMARDs) which include anti-TNF therapies, the world's largest selling class of drugs. Although anti-TNF therapies have improved the treatment and care for RA patients, only a subset of patients actually achieve remission to such therapy. On average 34% of patients achieve ACR50 response, or a 50% improvement of disease condition, based on peer-reviewed literature.[3-13]

In this paper, we introduce the PrismRA test, which predicts non-response to anti-TNF therapies. The PrismRA test will enable physicians to avoid prescribing anti-TNF therapy to patients that will not respond, allowing for alternative treatments to be prescribed instead. It will also ensure that the response rate in the patient population that is prescribed anti-TNF therapy is increased by removing non-responders. We review the clinical benefit of the test and financial impact to the insurance industry.

A decade of research to predict drug response in complex disease

When the Human Genome Project was initiated in 1990, the hope was that fully sequencing human DNA would elucidate all manner of disease information; however, it was quickly realized that many diseases are much more complex. Scientists and clinicians at Northeastern University and Brigham and Women's Hospital began to work on deciphering the biology of complex diseases in individual patients by superimposing gene expression data on the protein network of human cells to elucidate the active disease processes at the molecular level.[14,15] In doing so, they began to see novel patterns of disease biology, including drug response and non-response, which had never been described before. The ability to predict drug response in complex diseases provides a paradigm shift in how patients are treated using precision medicine.

The need to stratify patients with rheumatoid arthritis

RA is a chronic autoimmune condition characterized by inflammation of the joints resulting in bone damage, chronic pain and stiffness, loss of function, and disability.

Following failure of DMARDs to control disease, patients can be treated with biologic DMARDs. A class of biologic DMARDs known as anti Tumor Necrosis Factor (anti-TNF) inhibitors, have been introduced over the past fifteen years, completely changing autoimmune disease management. For patients that respond, the clinical outcomes of such therapies can be dramatic, enabling patients to achieve the goal of low disease activity or remission. Unfortunately, only a subset of the patient population responds well to anti-TNF therapies. Additionally, the approval of new biologic DMARDs including anti-CD20, co-stimulation blockade and anti- IL6 therapy (**Appendix A**), have further increased the expectation of physicians and patients in terms of what can be achieved in quality of life improvement. However, physicians have no tools to predict which patient will respond to which treatment, leading to patients being treated empirically and sequentially, and not by determining their actual disease biology and how well it fits a particular therapy.

Even though there are several different therapies with different mechanism of actions, 91% of patients are prescribed anti-TNF therapy as first-line biologic DMARD treatment (**Figure 1**). Since the first line of treatment only works for a subset of patients, a large portion of patients are switched to a

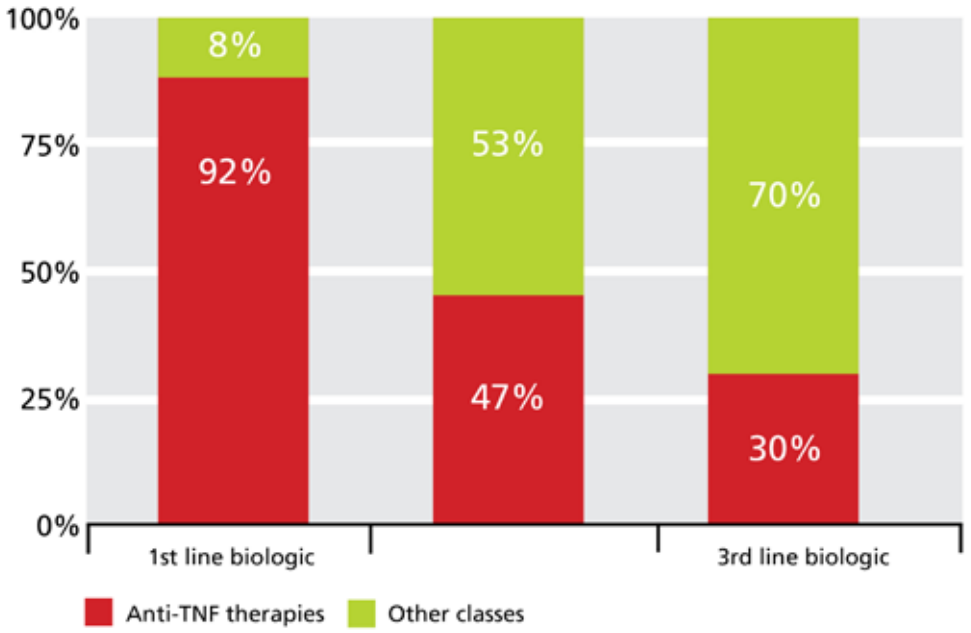


Figure 1: Current RA biologics treatment protocols, dominted by anti-TNF drugs[17]

different drug within nine-twelve months (second line). If the second line therapy fails too, then a third line of therapy will be initiated. Given the inability for physicians to determine if anti-TNF drugs will work before prescribing the therapy, there is a clear unmet medical need for a drug response test to help physicians avoid prescribing anti-TNF therapy to patients that will not respond. Determining non-responders upfront improves the response rate in the patient pool that is prescribed anti-TNF therapy. Ultimately, a test that can predict response (and non-response) to all existing therapies in the market would be most desirable.

The PrismRA test predicts non-response to anti-TNF therapy

PrismRA predicts non-response to all anti-TNF therapies including Humira, Enbrel and Remicade before the drug is prescribed. Currently, patients who are diagnosed with RA are prescribed a sequence of therapies, including anti-TNFs, without knowing if their disease is in fact driven by TNF related pathways and biology. Because up to 91% of patients are given anti-TNF therapy early in their disease progression, it is critical to know before the drug is prescribed which patients will not respond to anti-TNFs. The PrismRA test will enable physicians to avoid prescribing anti-TNF therapy to patients that will not respond, allowing for alternative treatments to be prescribed instead. It will also ensure that the response rate in the patient population that is prescribed anti-TNF therapy is increased by removing non-responders.

The PrismRA test applies a classifier based on the expression level of genes from whole blood RNA drawn prior to initiation of therapy. The classifier was developed by analyzing the gene expression data of cohorts from previous large scale clinical studies. The genes were identified based on their statistical significance of differential expression between the responder and non-responder populations. Selection of final genes was achieved by including only those genes that cluster on the protein network. Mapping the corresponding proteins onto the protein network uncovers the biology of responders and non-responders and explains why non-responders do not respond to anti-TNF therapy.

The accuracy of the final test result depends not only on the score of the classifier, but also on the threshold that is chosen. The threshold must balance the sensitivity, specificity and overall accuracy of the test and suitability for the intended use. The PrismRA test has been analytically validated in a CLIA laboratory. Preliminary performance specifications of PrismRA are a negative predictive value (NPV) of 92% and a true negative rate (TNR) of 50%, which means that PRISM RA predicts 50% of non-responders to anti-TNF therapy with a 92% accuracy. The next step is to validate the predictive accuracy of the test in a prospective clinical trial to give prescribing physicians confidence to use the test in their clinical practices. Scipher is engaged in active discussions with the rheumatology and payer community to determine the optimal clinical end points. Once the clinical trial achieves its end points, PrismRA will be offered commercially as a Laboratory Developed Test (LDT) in a CAP-proficient, CLIA-certified lab.

PrismRA requires the collection of one tube of blood during the pre-treatment screening regimen before initiation of biologic DMARD treatment. Results of the test will be returned to the physicians within 5-7 business days.

Removing ineffective therapy choices has many benefits for patients, providers, and payers in addition to reducing the direct cost of the drug. Eliminating drugs that patients will not respond to increases the overall efficacy rate of drugs used in this patient population. RA is a progressive disease that continues to worsen when a patient is prescribed an ineffective therapy, so it is imperative to use any tools available to make the best choice for therapy selection. As with virtually all drugs, particularly biologics, anti-TNFs therapies are

associated with a high rate of adverse events and co-morbidities, which should be avoided if the therapy is predicted to be ineffective in the patient.

A significant portion of patients don't respond to anti-TNF therapy, but are exposed to the side effects

The TNFα protein is a potent and central mediator of inflammation and microbial immunity, as well as many homeostatic physiological functions. It is the key target of anti-TNF drugs for the treatment of autoimmune diseases. TNF was discovered over 40 years ago and is expressed by monocytes, macrophages and activated T cells in response to endotoxins, as well as many non-immune cells. This pleiotropic role of TNF activation leads to a wide range of responses in diverse cell types, and hence explains why anti-TNF therapies have such important impacts on anti-inflammatory aspects of auto-immune diseases but also why they have such severe and debilitating side-effects.

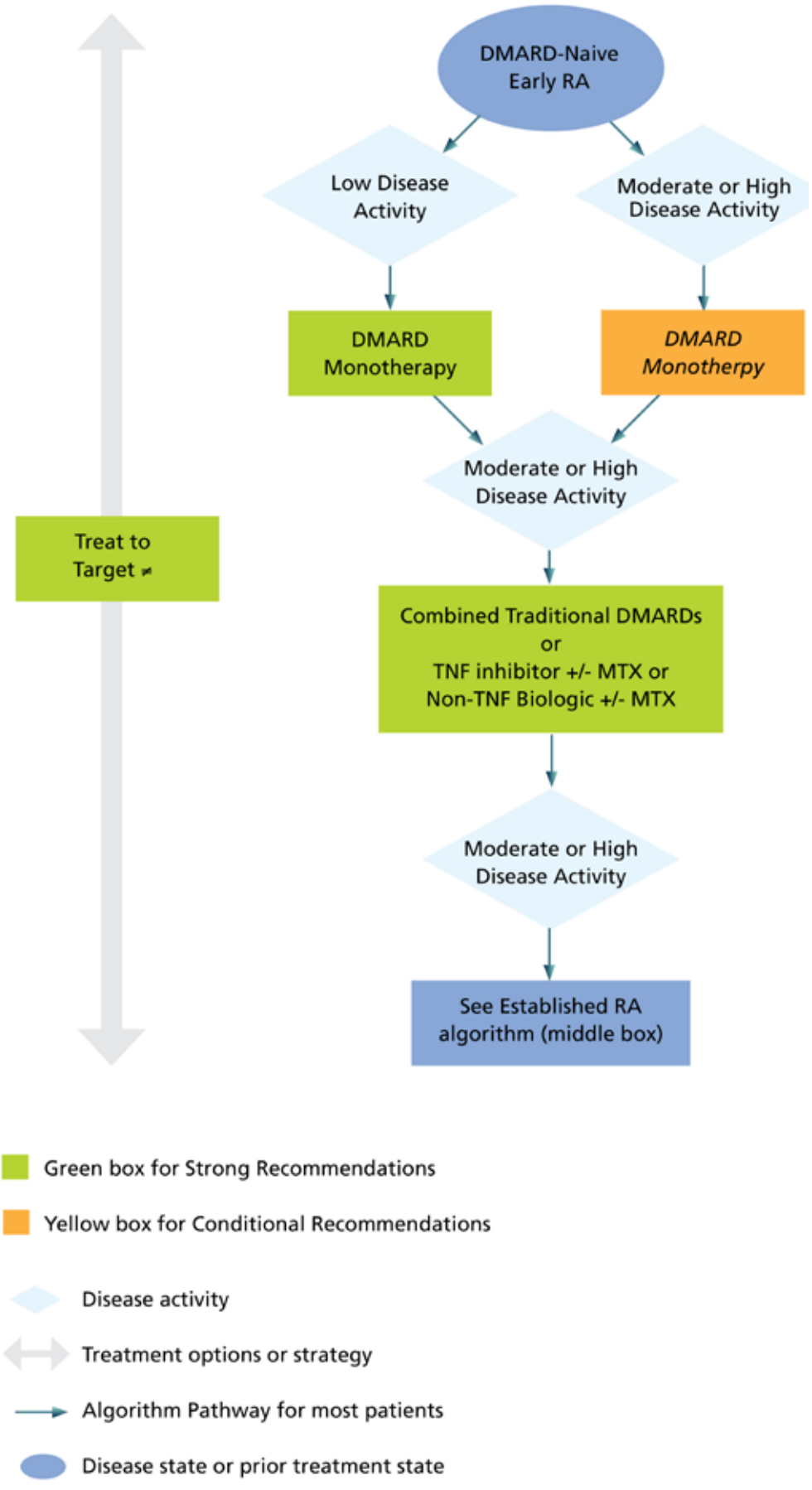
The ACR scoring system measures the amount of improvements in their patient's RA after being treated by medication. ACR20 represents a 20% improvement in disease condition on a scale that includes 28 designated joints, ACR50 represents a 50% improvement and ACR70 a 70% improvement. The ACR score takes into account factors such as inflammation (laboratory results), patient and physician assessment, pain assessment and a disability questionnaire.

Anti-TNF therapies have dramatically changed clinical management of patients with autoimmune diseases. When anti-TNF therapies were approved it was based on patients mainly achieving ACR20 criteria.[18] However, the current ACR treatment target is now assessed based on ACR50[19] and fewer patients reach this goal on anti-TNFs than achieved ACR20 in the pivotal registration trials that drove the approval of these agents. Claxton et al. presented anti-TNF efficacy

Stopped therapy due to adverse events	10%
Infusion or injection site reactions	3 to 20%
Drug-related lupus-like reaction	1%
Serious infections	3%
Tuberculosis	0.05%
Non-Hodgkin's lymphoma	0.06%

Figure 2: Safety/toxicity of anti-TNFs[22]

Figure 3: ACR treatment recommendation Treatment for RA usually is initiated with non-biologic DMARDs. However, when symptoms, persist, the 2015 ACR guidelines recommend:



rates by degree of ACR response based on reported trial data showing that monotherapy or combined therapy with biologics achieves 22-42% or 20-39.1% ACR50 response and 6-25% or 10-21% ACR 70 response after 6 months, respectively.[20] When collating ACR50 response rates from peer-reviewed literature that examines those values for ant-TNF therapies, we see an average 34% response rate. Additionally, a number of patients lose response after a period of time due to several factors. These include patient compliance with medication regimen, effective therapeutic drug levels reached in an individual and development of neutralizing antibodies to the medication.[21] These factors can differ among the unique molecular entities even within the same class of drugs. As seen in table of Appendix A, there are many molecular constructs within the same class of drug. Thus, the immunogenic response and pharmacodynamics/pharmacokinetics for each molecule will be unique.

Since anti-TNF treatment is immunosuppressive, patients should be screened for TB and Hepatitis B virus, and appropriately treated for these conditions if tests return positive. It is also important to ensure that patients are up to date on immunizations, particularly those against influenza, pneumococcal infection, and human papillomavirus infection.18. Live vaccines are contraindicated while patients are on anti-TNF therapy and for 1 month after stopping therapy. Anti-TNF agents are used with caution in patients with a history of malignancy. Other potential adverse effects of anti-TNF therapy include acute infusion reactions, which occur in approximately 10% of patients treated, and serious infusion reactions including anaphylaxis, convulsions, and hypotension, which occur in approximately 1% of patients receiving intravenous monoclonal antibodies. Injection site reactions can also occur with subcutaneously administered anti-TNF agents.

Appendix A: Biologic drugs approved for the treatment of RA

Name	Brand Name	Target	Molecular Construct	Route of Administration
Abatacept	Orencia	T-cells	Fc region of the immunoglobulin IgG1 fused to the extracellular domain of CTLA-4	IV/SC
Adalimumab	Humira	Anti-TNFα	Fully human mAB	SC
Adalimumab biosimilar (not USA)	Amjevita	Anti-TNFα		SC
Anakinra	KIneret	IL-1 Receptor agonist	Recombinant, non-glycosylated version of human IL-1RA	SC
Etanercept	Enbrel	Anti-TNFα	TNF receptor-IgG fusion protein	SC
Etanercept biosimilar (not USA)	Ereizi	Anti-TNFα		SC
Rituximab	Rituxan	Anti-CD20	Chimeric mAB	IV Infusion
Infliximab	Remicade	Anti-TNFα	Mouse-human chimeric mAB	IV
Infliximab biosimilar	Inflectra Renflexis	Anti-TNFα		IV
golimumab	Simponi Simponi Aria	Anti-TNFα	Human mAb	SC, IV
certolizumab pegol	Cimzia	Anti-TNFα	Pegylated Fab fragment of humanized mAb	SC
tocilizumab	Actemra	Anti-IL6R	Humanized mAb	IV infusion, SC
Sarilimumab	Kevzara	Anti-IL6R	Humanized mAb	SC

Other possible adverse effects include neutropenia, hepatotoxicity, serum sickness, leukocytoclastic vasculitis, rash including psoriasiform rash, demyelinating disorders. Drug-induced lupus has also been observed. If a patient develops a psoriasiform rash, this almost always resolves with cessation of the anti-TNF agent. If another anti-TNF agent is initiated, the risk of recurrence of the adverse event is approximately 50%. Serious infections occur in 2–4% of patients treated with anti-TNF therapy.

American College of Rheumatology guidelines support alternative therapies for treating RA

American College of Rheumatology (ACR) recommends[19] that the primary target for treatment of RA should be low disease activity or a state of clinical remission. Main goals of the guidelines include a treating to target approach for early and established RA patients, with a goal of achieving an ACR of 50 or 70. The primary goals of treating RA patients is to maximize long-term health-related quality of life through control of symptoms, prevention of structural damage, normalization of function and participation in social and work-related activities; and treatment to target by measuring disease activity and adjusting therapy accordingly optimizes outcome in RA.

Advances in drug development and improved understanding of the disease have further aided in the ability of the international rheumatology community to define a treatment target and therapeutic adaptations to reach it. An example is the ACR treatment recommendation decision tree below.[19]

If disease activity remains moderate or high despite DMARD monotherapy (with or without glucocorticoids), use combination DMARD or a TNFi or a non-TNF biologic

(all choices with or without MTX, in no particular order of preference), rather than continuing DMARD monotherapy alone (PICO A.7)

The guidelines specifically address the use of non-TNF biologics, and several such therapies have been proven to be effective and are approved for the treatment of RA. As a result, PrismRA and the ability to predict non-response to anti-TNF therapy and move patients to other biologic DMARD therapies, fits into the recommended treatment algorithm defined by the ACR.

Health economic case for patient stratification in rheumatoid arthritis

The determination of non-response, as compared to response, to anti-TNF therapy is equally valuable from an economic perspective. Since anti-TNF therapies are assigned as a first-line biologic DMARD therapy in 91% of patients, the clinical utility lies in the rheumatologist's ability to not assign an anti-TNF therapy, thereby increasing both the response rate to anti-TNF therapy of the patient pool that is prescribed the therapy, and removing an ineffective therapy from the anti-TNF non-responders' treatment plan.

The removal of ineffective anti-TNF therapy is a driving factor in reducing medical waste in RA, whose drug spend makes up 25% of US specialty drug spend.[23] As anti-TNF the rapies have become more prolific, their costs have also risen considerably. The retail cost of Enbrel has increased 80.3% since 2013, exceeding $4,000 for a 30-day supply, while the price of Humira increased 68.7% to roughly $3,700 in the same time frame.[24] While those increases do not take into account rebates or discounts, the increases remain substantial even after adjusting for these variables. A recent analysis of both list and net price changes from 2009-2015 found that percentage increases in net prices for Humira and Enbrel increased at rates 12-15 times higher than general inflation in the same time period.[25] The rise in anti-TNF therapy prices stands in stark contrast to the response rates of these drugs at the levels meaningful in clinical practice today. The Institute for Clinical and Economic Review (ICER) recently concluded that anti-TNF therapies were not cost effective at their current price points. Furthermore ICER showed that anti-TNF drug costs would need to decrease in the range of 48-69% in order to become cost-effective at the commonlyaccepted Quality Adjusted Life Year (QALY) threshold of $100,000-$150,000 annually.[26]

Lastly, the costs of adverse events and comorbidities for patients on anti-TNFs compound the ineffectiveness of these therapies in a non-stratified patient population (current status quo). Recent robust data has emerged, determining the downstream costs of anti-TNF therapy dispensing from a payer perspective through collaboration with the WEA Trust, a non-profit health insurer in Wisconsin. Recently presented at ISPOR 2017, the results show that Emergency Room visit costs per dispense are $522, $256, and $190 for Cimzia, Humira, and Enbrel respectively. Total downstream costs defined as ER visits, Hospitalizations, and Ambulance Transport come to average $442 per dispense among the 3 anti-TNF therapies Cimzia, Humira, and Enbrel.[27] Together, this economic data creates a powerful argument for patient stratification in RA drug assignment, particularly from the insurer and patient perspective. Currently many non-responders continue to take anti-TNF therapy up to 12 months before switching to an alternative treatment costing payers tens of thousands of dollars annually in wasted prescription and treatment costs. While rarely discussed together, the patient suffers disease progression and adverse events during nonresponse to therapy, while the insurer bears the economic cost (and shares it with the patient, increasing financial toxicity).

Conclusion

The PrismRA test will give rheumatologists a stratification tool and scientific rationale to select therapies for RA patients ahead of therapy initiation. By identifying patients that will not respond to anti-TNF therapies, the response rates in the population that is prescribed the therapy would increase and non-responders can be offered alternative approved medications quicker than they would in current standard-of-care clinical practice. As a result, more RA patients will quickly achieve remission or good response (ACR50) than by following the current paradigm, resulting in improvements in patient outcomes and significant health cost savings. ■

References

1. PharmaPoint Global Data Report GDHC495DFR, 2014;
2. Rheumatoid Arthritis Treatment Costs, 2016. https://www.rheumatoidarthritis.org.
3. Van de Putte LBA, Atkins C, Malaise M, et al. Efficacy and safety of adalimumab as monotherapy in patients with rheumatoid arthritis for whom previous disease modifying antirheumatic drug treatment has failed. Annals of the Rheumatic Diseases. 2004;63(5):508-516. doi:10.1136/ard.2003.013052.
4. Keystone EC, Kavanaugh AF, Sharp JT et al. Radiographic, clinical, and functional outcomes of treatment with adalimumab (a human anti-tumor necrosis factor monoclonal antibody) in patients with active rheumatoid arthritis receiving concomitant methotrexate therapy: a randomized, placebo-controlled, 52-week trial. Arthritis Rheum 2004;50:1400–11.
5. Furst DE, Schiff MH, Fleischmann RM et al. Adalimumab, a fully human anti tumor necrosis factor-alpha monoclonal antibody, and concomitant standard antirheumatic therapy for the treatment of rheumatoid arthritis: results of STAR (Safety Trial of Adalimumab in Rheumatoid Arthritis). J Rheumatol2003;30:2563–71.
6. Breedveld F. C., Weisman M. H., Kavanaugh A. F., et al. The PREMIER study: a multicenter, randomized, double-blind clinical trial of combination therapy with adalimumab plus methotrexate versus methotrexate alone or adalimumab alone in patients with early, aggressive rheumatoid arthritis who had not had previous methotrexate treatment. Arthritis & Rheumatology. 2006;54(1):26–37.
7. Maini R, St Clair EW, Breedveld F, et al. Infliximab (chimeric anti-tumour necrosis factor alpha monoclonal antibody) versus placebo in rheumatoid arthritis patients receiving concomitant methotrexate: a randomised phase III trial. ATTRACT Study Group. Lancet. 1999;354:1932–1939.
8. St Clair EW, van der Heijde DMFM, Smolen JS, Maini RN, Bathon JM, Emery P, et al. Combination of infliximab and methotrexate therapy for early rheumatoid arthritis: a randomized, controlled trial. Arthritis Rheum. 2004;50:3432–43. doi: 10.1002/art.20568.
9. Schiff M, Keiserman M, Codding C, et al. Efficacy and safety of abatacept or infliximab vs placebo in ATTEST: a phase III, multi-centre, randomised, double-blind, placebo-controlled study in patients with rheumatoid arthritis and an inadequate response to methotrexate. Ann Rheum Dis. 2008;67(8):1096–1103. doi: 10.1136/ard.2007.080002.
10. Moreland LW, Schiff MH, Baumgartner SW, Tindall EA, Fleischmann RM, Bulpitt KJ. et al. Etanercept therapy in rheumatoid arthritis. A randomized, controlled trial. Ann Intern Med. 1999;130:478–86.
11. Bathon JM, Martin RW, Fleischmann RM, Tesser JR, Schiff MH, Keystone EC, et al. A comparison of etanercept and methotrexate in patients with early rheumatoid arthritis.

N Engl J Med. 2000;343(22):1586–1593. doi: 10.1056/NEJM200011303432201.

12. Klareskog L, van der Heijde D, de Jager JP, et al. Therapeutic effect of the combination of etanercept and methotrexate compared with each treatment alone in patients with rheumatoid arthritis: double-blind randomized controlled trial. Lancet 2004;363:675–81. doi:10.1016/S0140-6736(04)15640-7.
13. Weinblatt M., Schiff M., Goldman A., et al. Selective costimulation modulation using abatacept in patients with active rheumatoid arthritis while receiving etanercept: a randomised clinical trial. Annals of the Rheumatic Diseases. 2007;66(2):228–234. doi: 10.1136/ard.2006.055111.
14. Sharma A, Menche J, Kitsak M, Ghiassian SD, Vidal M, Loscalzo J, and Barabasi A-L. Uncovering disease-disease relationships through the incomplete human interactome. Science;347(6224):841.
15. Ghiassian SD, Menche J, Barabási A-L (2015) A DiseAse MOdule Detection (DIAMOnD) Algorithm Derived from a Systematic Analysis of Connectivity Patterns of Disease Proteins in the Human Interactome. PLoS Comput Biol 11(4): e1004120. doi:10.1371/journal.pcbi.1004120.
16. CDC, Rheumatoid Arthritis (RA), 2016. https://www.cdc. gov/arthritis/basics/rheumatoid.htm.
17. Christian et al., IR Thematic Call on Sarilumab. Regeneron investor presentation November 9th, 2015.
18. Humira (adalimumab) label – FDA, revised 12/2011. https://www.accessdata.fda.gov/drugsatfdadocs/label/2011/125057s0276lbl.pdf. Accessed January 3, 2018.
19. Singh JA et al., 2015 American College of Rheumatology guidelines for the treatment of rheumatoid arthritis. Arthritis Rheumatology 2016;68(1):1-26.
20. Claxton et al., An Economic Evaluation of Tofacitinib Treatment in Rheumatoid Arthritis: Modeling the Cost of Treatment Strategies in the United States. J Manag Care Spec Pharm. 2016;22(9):1088-1102.
21. Krishna M, Nadler SG. Immunogenicity to Biotherapeutics – The Role of Anti-drug Immune Complexes. Frontiers in Immunology. 2016;7:21. doi:10.3389/fimmu.2016.00021.
22. Siegel CA, et al. Inflamm Bowel Dis. 2010;16:2168-2172.
23. UnitedHealth Center for Health Reform & Modernization. Issue Brief. The Growth of Specialty Pharmacy: Current trends and future opportunities. April 2014. American Health & Drug Benefits. Trends in Biologic Therapies for Rheumatoid Arthritis. March/April, 2012.
24. "Rheumatoid arthritis drug prices on the rise", Modern Healthcare, April 1 2016.
25. Langreth R, Keller M, Cannon CP. Decoding Big Pharma's Secret Drug Pricing Practices. Bloomberg. June 29, 2016; https://www.bloomberg.com/graphics/2016-drug-prices/. Accessed December 22, 2016.
26. Institute for Clinical and Economic Review, 2017 Page ES24 Evidence Report: Targeted Immune Modulators for Rheumatoid Arthritis Table ES8
27. Hoffman et al, "Adverse Drug Event Data as a Proxy to Total Medical Costs of TNF alpha inhibitors", presented at ISPOR Annual Meeting, Boston May 2017.

Keith Johnson, Ph.D., *Author. Chief Scientific Officer of Scipher Medicine, 303 Wyman Street, Waltham MA 02145, USA. Email: keith.johnson@sciphermedicine.com

Michael Weinblatt, MD; John R. and Eileen K. Riedman Professor of Medicine Harvard Medical School. R. Bruce and Joan M. Mickey Distinguished Chair in Rheumatology Division of Rheumatology, Immunology and Allergy, Brigham and Women's Hospital, Boston, USA.