Pioneering precision medicine in rheumatoid arthritis

by **Johanna B. Withers PhD, S. Dina Ghiassian PhD, Slava Akmaev PhD, Alexis Gescheider, and Alif Saleh**

Introduction and background

Rheumatoid arthritis (RA) is a debilitating autoimmune disease affecting nearly 1.5 million Americans.[1] Medical guidelines for RA treatment recommend early therapeutic intervention, with the goal of reaching low disease activity or remission, to prevent irreversible joint damage.[2-6] Once limited by only one biologic therapy, providers now enjoy selecting from five different mechanisms of action as approved targeted disease modifying anti-rheumatic drugs (DMARDs) that modulate different aspects on inflammation. Despite having so many options, nearly 90% of patients still receive a tumor necrosis factor inhibitor (anti-TNF therapy) as their first targeted DMARD, in part because providers have had no means to assess a patient's likelihood of response to that line of therapy.

The use of anti-TNF therapy is a consequence of the disproportionate multi-payer U.S. reimbursement environment. The widespread prescription of a TNF inhibitor for RA patients is inconsistent with medical guidelines for treating RA patients; guidelines do not recommend one targeted therapy over another. Furthermore, the response rates for targeted therapies approved for treating RA are typically 30-40%.[7,8] As a result, many patients are receiving an expensive targeted DMARD that will not provide relief from the debilitating symptoms of RA. Once diagnosed with RA, there is a window of opportunity to gain control of the disease and avoid permanent joint damage and the myriad of costs and co-morbidities that come with a lack of adequate therapeutic response. Research shows that patients who do not have an adequate response to anti-TNF therapy have twice the number of joint replacement surgeries, emergency department visits, and inpatient hospitalizations in their first year of biologic treatment.[9] Furthermore, with uncontrolled inflammation and pain, RA patients oftentimes seek additional medications for symptom relief, many of whom are prescribed opioids, with 41% of patients reported as regular opioid users.[10,11]

Arthritis and rheumatoid conditions are costing the US economy more than $80

billion per year and anti-TNF therapies are the world's largest selling drug class.[12] However, this high cost of treating rheumatic diseases has not yielded corresponding improvements in patient outcomes.[13,14] Therefore, patients and the healthcare system are spending millions of dollars on drugs that are not getting RA patients to their treatment targets.

With many nearly equivalent treatment options, it is unclear which drug will be most effective for an individual patient's disease biology, and valuable time may be spent trying multiple therapies that do not get a patient to reach his or her treatment targets.[15] The lack of drug response biomarkers for stratification of individual patients for available therapies has been cited as a major weakness of current RA treatment regimens[6] and highlights the urgent need for precision medicine tools to guide the treatment of patients with RA.

Scipher Medicine is a spin-out of Northeastern University founded on the basis of, first, building a map of human biology called the Human Interactome that explains how proteins expressed from genes interact to cause specific disease phenotypes (see on more below Human Interactome) and, second, developing computational tools needed to interpret the genetic list developed by the Human Genome Project (see more below on Network Medicine). Building on that founding work, Scipher Medicine developed PrismRA® as a new molecular signature test that assesses the likelihood that a patient with RA may not respond to an anti-TNF therapy before said patient starts a targeted treatment for the first time.

The Human Interactome is a map of human biology and provides insights into disease pathogenesis

One challenge of studying human biology is devising strategies to integrate information from diverse sources of data to gain insights into disease biology that could be used for therapeutic indications. This is particularly true of diseases such as RA where disease pathogenesis is a complex interplay of genetic and environmental factors.[16] Scipher Medicine has taken an alternative approach, using network medicine to better understand human disease, identify and decipher individuals' unique molecular signatures, stratify patients, and provide guidance for treatment.

Network medicine is the study of complex interaction patterns of biological entities, where network topology and dynamics are applied to the understanding, prevention, and treatment of human disease. To shed light on the molecular networks that underlie human biology, researchers at Scipher Medicine overlaid its proprietary molecular technology platform onto the experimentally validated Human Interactome map and identified the reference maps of cellular biology of RA and other complex diseases; in general, these maps serve as the basis for interpreting the Human Interactome (see **Figure 1**).

In this paper, we discuss our use of a computational reference map that incorporates information about protein interactions from more than 90% of all known human proteins. Researchers have shown that proteins associated with a disease tend to cluster in modules when mapped onto the Human Interactome.[17,18] Scipher Medicine developed a module associated with RA that guided development of the PrismRA® molecular signature test which determines whether a patient is unlikely to respond to anti-TNF therapies.

PrismRA® is a first-of-its-kind molecular signature test based on knowledge derived from network medicine and the Human Interactome

Artificial intelligence and machine learning tools were designed and trained to identify complex data patterns to stratify patients. We undertook to identify a pattern in RA patient data consistent with suboptimal response to anti-TNF therapies using three sources of data: functional expressed single-nucleotide sequence variations, RNA gene expression levels, and clinical assessments of disease-relevant patient characteristics.

Furthermore, we note that no single clinical variable in isolation (including DNA or RNA) may be able to accurately separate those patients who are likely to respond to anti-TNF therapies from those who are unlikely to respond. The PrismRA® molecular signature test includes 23 different assessments. By using this combination of molecular biomarkers that lie close to the RA disease module with disease-relevant clinical assessments, Scipher's machine learning algorithms identified a pattern in patient data that stratifies patients according to their likelihood of inadequate response to anti-TNF therapies with 90% accuracy.

Incorporation of PrismRA® into the clinical management of RA can improve the care of all RA patients taking their first targeted therapy, not just the predicted non-responders to anti-TNF therapies. Patients who inadequately respond to anti-TNF therapies should avoid this drug class and be directed to other treatment options to ameliorate the signs and symptoms of RA and prevent potential structural joint damage. As a result of this redirection of predicted non-responders, the patients prescribed an anti-TNF therapy as their first targeted DMARD will have a greater likelihood of response. In the study that validated the performance of the PrismRA® molecular signature test, Scipher predicted that the fraction of the RA patient population who responded to their first targeted DMARD could have increased by 40% (see **Figure 2**).[19] In other words, before PrismRA® approximately 30 out of 100 patients respond to anti-TNF therapy, now, with clinical use of PrismRA® 42 patients out of 100 respond to their first targeted therapy. This represents a significant improvement in the response rate for first-line therapy.

Conclusions

PrismRA® streamlines treatment options for RA patients and provides patient-specific data to the treating rheumatologist that can help guide treatment decisions. Patients identified as non-responders to anti-TNF therapies are directed to an alternative drug class approved as a first-line targeted therapy to which they have a better chance at reaching their treatment targets. Both the predicted non-responders and the remaining patient population experience enriched response rates to therapy, thereby raising the overall first-line targeted therapy response rate in RA. From an economics perspective, PrismRA® will save millions of dollars that are currently being spent on expensive drugs that are not helping patients reach their treatment targets.

At this point PrismRA® has been validated for anti-TNF therapies only, however, Scipher's network medicine approach could be applied to develop diagnostics for other targeted DMARDs. This approach gives a patient the opportunity to reach treatment targets earlier and impacts many aspects of patient care, especially when the correct targeted therapy is prescribed as a first-line choice. Access to alternative approved therapies is then optimized accordingly, thereby reducing the administrative burden for rheumatology practices, improving the response rates, and suppressing disease progression. JoPM

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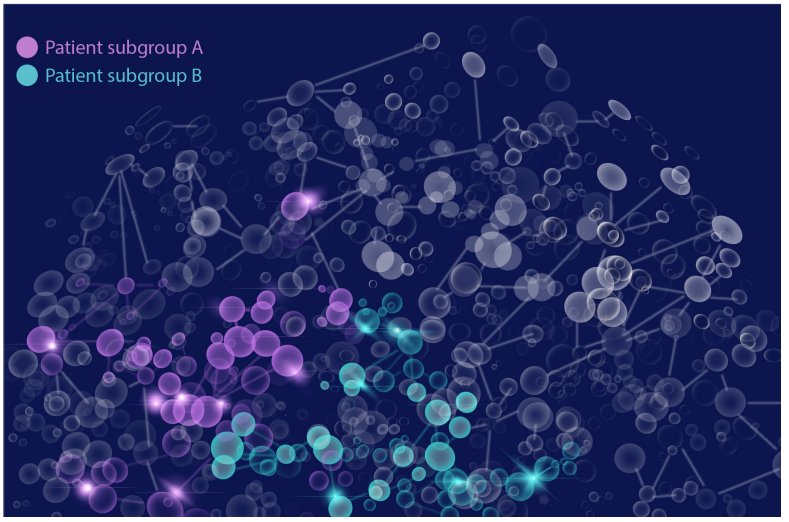


Figure 1: The Human Interactome is a map of protein-protein interactions between approximately 18,500 of the estimated 20,000 proteins encoded by the human genome. Each protein (circle) in the interactome forms a molecular interaction (line) with at least one other protein to generate a network of connections. Superimposing individual patients' RA disease biology identifies molecular differences between those patients who are likely to respond and not respond to anti-TNF therapies (purple vs blue).

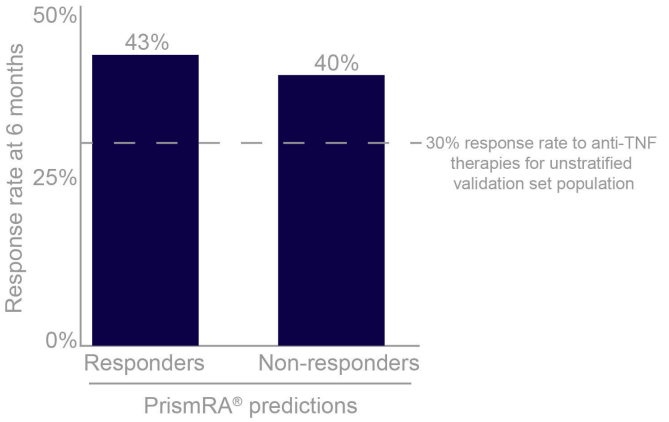
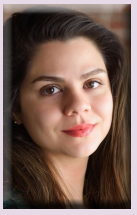


Figure 2: The PrismRA® test has the potential to enhance response rates for first-line biologic treatments for RA patients by 40%. Patients who are predicted responders had an observed response rate to anti-TNF therapies of 43%. Patients who are predicted non-responders should be directed to alternative mechanisms of action that have reported response rates around 40%. With PrismRA®, both predicted responders and non-responders have a greater likelihood of responding to their first biologic or targeted treatment.

Alif Saleh, CEO
A global business leader and entrepreneur at heart, Alif draws from his scientific background in systems biology, network theory, and engineering at Scipher. Alif has successfully led cross-disciplinary teams in technology and business across Asia, Europe and the Americas – raising over $225 million in venture and private equity capital. Previously with BCI (acquired 2000), Alfa Laval (IPO 2002), and Myriant (acquired 2014), Alif received his MSc degree in Chemical and Genetic Engineering from Lund Institute of Technology, Sweden.

Slava Akmaev, PhD
Chief Technology Officer
Slava is a recognized leader in the adoption of the AI/ML technology in healthcare and drug development and is a frequent speaker at some of the most prolific industry events. Slava is the inventor on a number of issued and pending patent applications and has published articles in computational biology, artificial intelligence and molecular biology. Prior to Scipher Medicine, Slava developed and launched a number of commercial diagnostic tests in oncology, reproductive health and rare diseases. Dr. Akmaev holds a PhD in Applied Mathematics from the University of Colorado at Boulder.

Alexis Gescheider
Director of Marketing
Alexis expertly constructs marketing teams and programs to connect and cultivate audiences, and builds recognized brands from start-ups to Fortune 500 companies. She brings a patient-centered approach to marketing, understanding the importance for people to be engaged and informed in their healthcare decisions. In her previous role at PatientsLikeMe, the world's largest personalized health network, she built creative member experiences to engage members in the healthcare journey, and partnered with life science companies to create innovative patient centered research to speed innovation and inform decision making.



Dina Ghiassian, PhD
Director of Systems Biology and Network Medicine
Dina is a Systems Medicine enthusiast and has been applying AI/ML technology and graph theory on clinical and molecular data to develop diagnostic products and predict therapeutic opportunities.
Working with Dr. Albert-Laszlo Barabasi and Dr. Joseph Loscalzo, Dina has led the work of applying data and network science in medicine and developed a suite of tools that are used by scientists and engineers across the world to improve the understanding of complex diseases, patient drug response and drug mechanism of action. Dina is the inventor of couple of pending patent applications and published key peer-reviewed papers with more than 1800 citations. Dina continues to explore the frontier of what predictive models can achieve in medicine using her and Scipher's unique multidiscipline approach including machine learning, graph theory, bioinformatics, and medicine. She received her PhD in Physics from Northeastern University's Center for Complex Network Research.

Johanna Withers, PhD
Principal Scientist
Johanna brings expertise in RNA and molecular biology to Scipher Medicine. Working at Yale University with Joan Steitz, Johanna's postdoctoral research described how viruses use long noncoding RNAs to manipulate host cells. Now, she is leveraging the power of network medicine to direct the development of precision medicine tools in autoimmune diseases. Johanna received her PhD in Cell, Molecular, Developmental Biology and Biophysics from the Johns Hopkins University.