What Precision Medicine Might Mean for Your Rheumatoid Arthritis Journey

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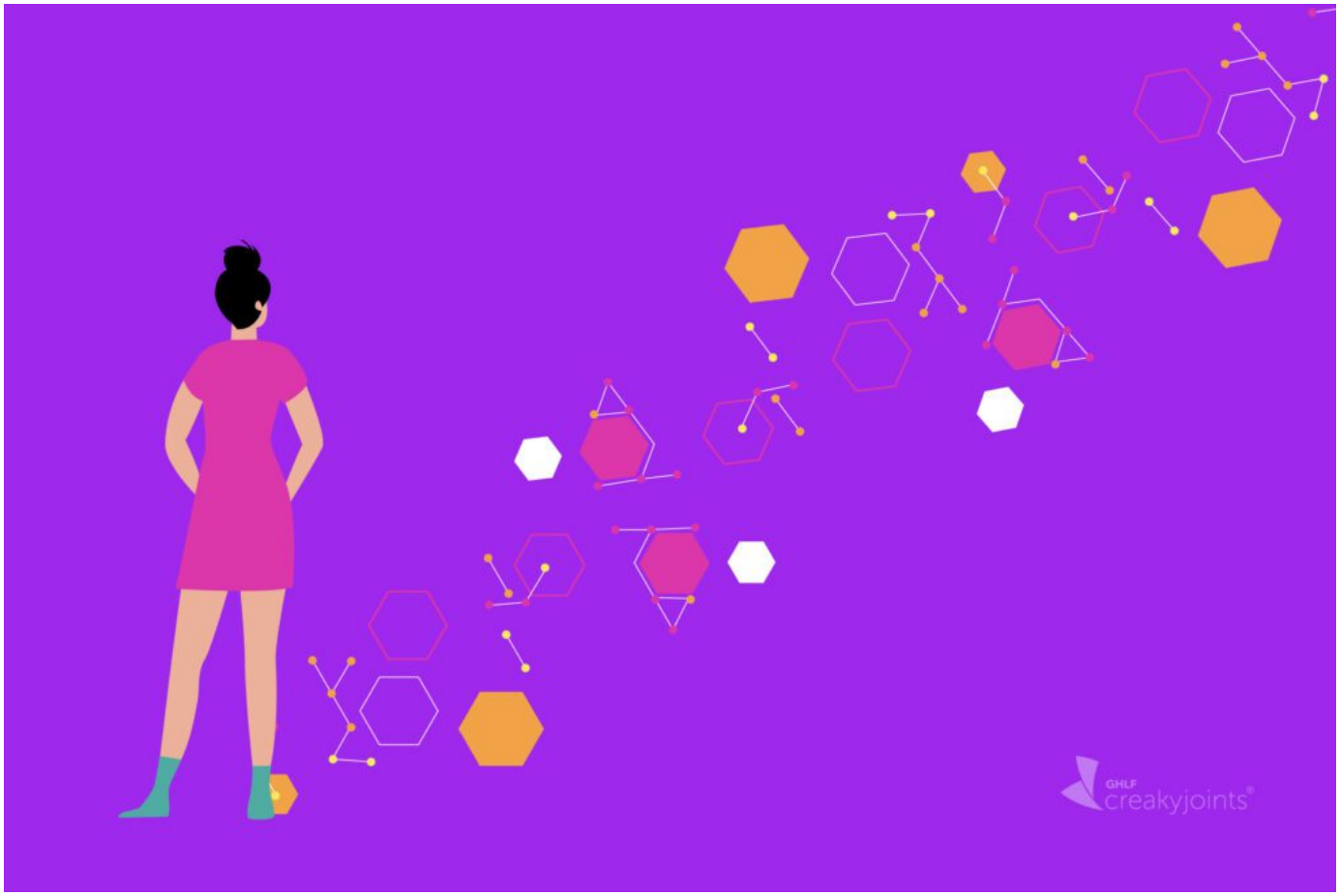
Learn about new advances that could help provide hope for pinpointing the right RA treatment — without the drawn-out trial and error.

Check out "Your Guide to Precision and Personalized Medicine for Rheumatoid Arthritis" (https://precisionandpersonalizedmedicine.creakyjoints.org/)for more information on this topic.



(https://creakyjoints.org/wp-content/uploads/2022/10/WHAT-PRECISION-MEDICINE-MIGHT-MEAN-FOR-YOUR-RA-JOURNEY2logo-1024x683.jpg)

Credit: Tatiana Ayazo

Some rheumatoid arthritis (RA) patients get lucky: They get diagnosed quickly, start on a medication (usually methotrexate), and it works really well without causing too many side effects. The runners-up require the addition of a biologic to control more active disease, but the first drug they add turns out to be effective and tolerable.

For many people with RA, unfortunately, pinpointing the right treatment is far more challenging.

The main problem, says J. Eugene Huffstutter, MD, (https://www.arthritisassociateschatt.com/our-providers/j-eugene-huffstutter-md/) a rheumatologist with Arthritis Associates in Hixson, TN, is that RA is not a homogeneous condition, meaning it's likely driven by a number of different inflammatory pathways in various subgroups of patients — yet there isn't any way to identify and sort them in this manner.

Patients often go through a drawn-out experimental process, trying one drug after another until they hopefully, eventually, find a good fit. This kind of trial and error can take months, if not years.

Understanding Rheumatoid Arthritis Treatment Options

Today's RA patients have numerous medications to choose from, ranging from conventional synthetic disease-modifying anti-rheumatic drugs (DMARDs) like methotrexate and sulfasalazine to biologic DMARDs such as tumor necrosis factor (TNF) inhibitors like infliximab (Remicade) and etanercept (Enbrel) as well as newer targeted DMARDs such as Janus kinase (JAK) inhibitors like baricitinib (Olumiant) and tofacitinib (Xeljanz).

Other options include abatacept (Orencia), which blocks T cells; rituximab (Rituxan), which blocks B cells; and anakinra (Kineret), which blocks interleukin-1 (IL-1). Biosimilars, which are highly similar to biologics, are becoming more available. To learn more, download our free Patient's Guide to Understanding Biosimilars (https://creakyjoints.org/education/a-patients-guide-to-understanding-biosimilars/,).

Choosing, however, isn't easy. TNF inhibitors can be very effective, but they only work for about 50 to 60 percent of rheumatoid arthritis patients (https://bmcmusculoskeletdisord.biomedcentral.com/articles/10.1186/s12891-021-04248-y). ACR suggest starting with methotrexate alone and then adding a biologic in the TNF inhibitor class if a patient does not quickly reach low disease activity.

When a TNF inhibitor fails, patients either try a second TNF inhibitor (depending on what their doctor recommends and their insurance company requires) or move on to a drug in a different class — which may or may not work for them. Some cycle through several medications before finding the right one, and "about 12 to 25 percent of patients don't respond to any RA drug" that's currently on the market, says Harris Perlman, PhD, (https://www.feinberg.northwestern.edu/faculty-profiles/az/profile.html?xid=12783) Chief of Rheumatology at Northwestern University Feinberg School of Medicine.

"We waste about $3 billion a year due to trial and error," he says, adding that this process also leads to poorer health outcomes as patients spend longer periods in high-disease activity or end up relying on steroids.

Patients, understandably, are also frustrated. "The current process is awful. Going through periods of trial and error has been exhausting, both mentally and physically," says Seth Leibowitz, who has had to change medication numerous times since he was first diagnosed in 2008. "If there was a way to match my subtype of RA to the right medication [so I wouldn't have to experiment to see what works], I would be beyond happy."

Thanks to advances in precision medicine, this kind of predictive match-making could soon become a reality.

Moving Toward Tailored Treatment

Precision medicine is sometimes called personalized medicine, but it goes beyond choosing a treatment based on patient preference or whether someone has a comorbid condition like heart disease. Instead, precision medicine uses information about a patient's genes, proteins, or other objective characteristics to identify the treatment that is best suited to them.

Rheumatologists interested in precision medicine point to how it has transformed cancer care in only a few decades. No longer are cancer patients treated with a one-size-fits-all approach; instead, they're tested for genetic changes and biomarkers (biological molecules found in blood or other fluids or tissues) and treated for accordingly.

A breast cancer patient who is “estrogen receptor positive,” for instance, would be given a therapy that blocks the hormone fueling their cancer. Those who are “estrogen receptor negative,” in contrast, skip such hormonal treatment, but even knowing what to pass on is beneficial: “You’re not losing time giving someone drugs that aren’t going to work for them,” says rheumatologist Isabelle Amigues, MD, assistant professor at National Jewish Health in Denver, CO.

“Precision medicine for RA is not quite ready for prime time the way it is for cancer, but we are making progress,” says Huffstutter. In particular, he believes that certain patients might benefit from knowing about a test called PrismRA (https://www.prismra.com/about-prismra/resources/), a blood test that combines a biomarker panel with a machine learning-based algorithm. In short, it analyzes 23 biological features including 19 gene expression features and four clinical and laboratory measures and uses that information from a patient’s blood sample to predict whether a patient is unlikely to respond to a TNF inhibitor.

Although some research on the test is ongoing — Huffstutter and Amigues are among providers that are continuing to share deidentified patient data with the test’s manufacturer, Scipher Medicine. Huffstutter is confident that PrismRA provides patients who are at a crossroads with information that can help guide them.

Research has shown that PrismRA can predict with 90 percent accuracy (https://www.prismra.com/about-prismra/faq/) who will *not* respond to TNF inhibitor DMARD therapies with a test result of inadequate response and would therefore be better off choosing a different type of medication. Providers who order the test for a patient do not need to have an in-house lab; they simply mail a blood sample into the company for processing, he adds.

Huffstutter does not believe the test is appropriate for most brand-new patients, because starting on methotrexate — which is inexpensive and has a long track record — is still the first-line go-to therapy. But when a patient does not respond sufficiently to methotrexate, or can’t take it for some reason, the PrismRA test can be very helpful, he says.

Amigues agrees that the test is useful for this purpose. “I order it for patients who are biologic naïve,” meaning they’ve never taken a biologic drug before but are considering starting, she says. “The goal is to put a patient into disease remission as fast as possible. If you have a blood test that says that person will *not* respond to a TNF inhibitor, you would not start them on one,” and instead try a drug with a different mechanism of action.

Research (https://www.tandfonline.com/doi/full/10.1080/14712598.2022.2066972) has shown that patients who use PrismRA to inform their treatment choice have better outcomes: Those with high disease activity who took the test, learned that they were *not* likely to respond to a TNF inhibitor, and started a non-TNF treatment were almost twice as likely to have greater improvement in CDAI (Clinical Disease Activity Index) scores compared to those who followed the standard protocol of just trying a TNF inhibitor without knowing whether it would work for them.

Additional Advances on the Horizon

Scipher Medicine is also working to launch a version of the PrismRA test that predicts response (instead of non-response) to the drug as well as a test for T-cell and Jaki classifiers and IL-6.

Other scientists outside of Scipher Medicine have explored developing different blood tests that can predict whether an RA patient will respond to a TNF inhibitor, but at the moment the PrismRA test is the only commercially-available test of this sort.

Researchers (https://www.ncbi.nlm.nih.gov/pmc/articles/PMC8995470/) have also identified a slew of biomarkers that might one day be used to predict whether someone will respond to different drugs such as methotrexate, abatacept, or rituximab, but again, no such tests are currently available.

While blood-based tests are certainly easy to use and it’s possible that more of them will eventually hit the market, other researchers are instead aiming to develop tests that rely on synovial (joint) tissue biopsies. Although obtaining this tissue is more complicated than getting a blood test — you’d need to undergo an

ultrasound-guided needle biopsy — Perlman believes that more accurate information about what's driving someone's RA can be gleaned from this process.

Several international scientists have been exploring this approach. One study, presented at the 2019 annual American College of Rheumatology meeting (https://acrabstracts.org/abstract/a-randomised-open-labelled-clinical-trial-to-investigate-synovial-mechanisms-determining-response-resistance-to-rituximab-versus-tocilizumab-in-rheumatoid-arthritis-patients-failing-tnf-inhibitor-t/), found that patients whose synovial tissue biopsies had fewer B cells responded better to tocilizumab (Actemra) than to rituximab.

Now a group of U.S.-based scientists, led by Perlman's team at Northwestern and funded by the National Institute of Arthritis and Musculoskeletal and Skin Diseases, are taking it a step further. They're aiming to create genetic signatures based on joint tissue biopsies that could be used to predict whether a patient will respond to any RA drug on the market.

What This Means for You

Whether you are newly diagnosed, living with RA for a few years, or many years – understanding the strides being made in precision medicine can help you have more informed conversations with your doctor and greater shared-decision making when deciding on your course of care.

"When I think about precision medicine, it's twofold," says rheumatologist Grace C. Wright, MD, PhD, (https://awirgroup.org/about/about-awir/22-grace-c-wright.html) Founder and President of the Association of Women in Rheumatology (AWIR). "It's about taking the tools that we currently have available to make the right diagnosis. Because if I miss the diagnosis than everything else is moot. So there's precision in the diagnosis, and then precision in the care — and the precision there says how can I choose the best therapy that allows this person to have the greatest chance of success," says Dr. Wright.

This article is part of "Your Guide to Precision and Personalized Medicine for Rheumatoid Arthritis" and was made possible with support from Scipher Medicine.

+ Sources

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Suggested Reading

What I Lost (And Now Gained) Because of Rheumatoid Arthritis (https://creakyjoints.org/about-arthritis/rheumatoid-arthritis/ra-patient-perspectives/what-i-lost-and-gained-from-ra/)

The Journey to Find the Right Treatment for Rheumatoid Arthritis (https://creakyjoints.org/about-arthritis/rheumatoid-arthritis/ra-treatment/the-journey-to-find-right-ra-treatment/)