Personalized Medicine in Rheumatology: Tomorrow’s Promise or Today’s Reality?

Certified CME

John S. Sundy, MD, PhD (Chair)
Associate Professor of Medicine
Duke University Medical Center

S. Louis Bridges, Jr., MD, PhD
Professor of Medicine
University of Alabama at Birmingham

Daniel E. Furst, MD
Professor of Medicine
University of California, Los Angeles

Philip J. Mease, MD
Director of Rheumatology Research
Swedish Medical Center
Clinical Professor
University of Washington School of Medicine

Jointly sponsored by

Duke School of Medicine
The Institute

Commercial Support Acknowledgement:
This CME activity is supported by educational grants from Abbott, Amgen, Bristol-Myers Squibb, and UCB.
The pace of drug development in rheumatic diseases continues to speed along, with numerous biologic agents having received approval from the U.S. Food and Drug Administration alone in the last decade for conditions such as rheumatoid arthritis, psoriatic arthritis, and ankylosing spondylitis. Research regarding the utility of these agents, as well as those in late-stage clinical development, dominates the pages of many peer-reviewed journals and headlines discussions at most of the frequently attended sessions at annual rheumatology meetings. While acknowledging the likelihood that personalized medicine will play a significant role in the overall management of patients with rheumatic diseases within the next five years, many rheumatologists are unaware of the specific ways that research groups are preparing for its arrival. Skepticism, although sometimes valid, remains regarding the potential applicability of specific biomarker assays and genetic testing in rheumatology. Furthermore, the vocabulary of biomarkers is unfamiliar to many practicing rheumatologists.

Target Audience
The target audience for this activity is comprised of U.S.-based practicing rheumatologists.

Learning Objectives
- Discuss key factors that continue to drive research into personalized medicine across the healthcare spectrum, with a specific focus on rheumatology
- Describe several primary ways in which further understanding of the role of biomarkers and genetic profiles in rheumatic diseases will help to individualize patient care
- Analyze currently published data related to biomarker and genetic research, identifying both its potential impact on patient care and its flaws

Faculty
John S. Sundy, MD, PhD (Chair)
Associate Professor of Medicine
Duke University Medical Center
Durham, North Carolina

S. Louis Bridges, Jr., MD, PhD
Professor of Medicine
Department of Medicine
University of Alabama at Birmingham
Birmingham, Alabama

Daniel E. Furst, MD
Professor of Medicine
University of California, Los Angeles
Los Angeles, California

Philip J. Mease, MD
Director of Rheumatology Research
Swedish Medical Center
Clinical Professor
University of Washington School of Medicine
Seattle, Washington

Staff and Content Validation Reviewer Disclosure
The staff involved with this activity and any content validation reviewers of this activity have reported no relevant financial relationships with commercial interests.

Resolution of Conflicts of Interest
In accordance with the ACCME Standards for Commercial Support of CME, the Duke University School of Medicine implemented mechanisms prior to the planning and implementation of this CME activity to identify and resolve conflicts of interest for all individuals in a position to control content of this CME activity.

Planning Committee/Faculty Disclosure
The following speakers and/or planning committee members have indicated that they have no relationship(s) with industry to disclose relative to the content of this CME activity: S. Louis Bridges, Jr., MD, PhD

The following speakers and/or planning committee members have indicated that they have relationship(s) with industry to disclose:
John S. Sundy, MD, PhD, has indicated that he is an advisory board member for Ardea Biosciences. He is a consultant for Novartis, Nuon Therapeutics, Inc., Pharmos Corporation, Regeneron, and Savient Pharmaceuticals. He is a principal investigator for Ardea Biosciences, Celgene, Metabolix, Inc., Nuon Therapeutics, Inc., Regeneron, and Savient Pharmaceuticals.
Daniel E. Furst, MD, has indicated that he is an advisory board member for Abbott, Actelion, Amgen, Biogen Idec, Bristol-Myers Squibb, Centocor, Genentech, Gilead, GSK, NIH, Novartis, Pfizer, Roche, and UCB. He is a consultant for Abbott, Actelion, Amgen, Biogen Idec, Bristol-Myers Squibb, Centocor, Genentech, Gilead, GSK, NIH, Novartis, Pfizer, Roche, and UCB. He is a speaker for Abbott, Actelion, and UCB.

Philip J. Mease, MD, has indicated that he is a consultant speaker and research contractor for Abbott, Amgen, Biogen Idec, Bristol-Myers Squibb, Centocor, Eli Lilly, Genentech, Novartis, Pfizer, and UCB.

Unapproved Use Disclosure
Duke School of Medicine requires CME faculty to disclose to attendees when products or procedures being discussed are off-label, unlabeled, experimental, and/or investigational (not FDA approved); and any limitations on the information that is presented, such as data that are preliminary or that represent ongoing research, interim analyses, and/or unsupported opinion. This information is intended solely for continuing medical education and is not intended to promote off-label use of these medications. If you have questions, contact the medical affairs department of the manufacturer for the most recent prescribing information.

Disclaimer
The information provided at this activity is for continuing education purposes only and is not meant to substitute for the independent medical judgment of a healthcare provider relative to diagnostic and treatment options of a specific patient’s medical condition.

Instructions on How to Receive Credit
Participants must review the materials on accreditation information, target audience, learning objectives, and disclosure information.

Then Earn CME Credit Online in Three Easy Steps!
To earn up to 0.75 AMA Category 1 Credits™ follow these three easy steps:
1. Go to www.pmhrheum.com
2. Follow the on-screen instructions to access the post-test and evaluation
3. After passing the post-test, print out your electronic CME certificate
In order to successfully complete this activity for AMA PRA Category 1 Credit™, learners must achieve a minimum of 80% on the post-test.
Personalized medicine has the potential to revolutionize current rheumatology practice.

With noninvasive biomarker assays that predict response or non-response to therapy, rheumatologists will be able to prescribe the right treatment for the right person at the right time. In addition, tests of disease susceptibility and preclinical disease activity will allow clinicians to identify patients who may benefit from increased monitoring and risk-factor reduction. With the development of new biomarker assays, rheumatologists and other healthcare providers (HCPs) must prepare for the growth of personalized medicine in the rheumatology clinic.

Personalized Medicine in Rheumatology: An Overview

The goal of personalized medicine is to enable rheumatologists to more precisely select drug therapies and doses tailored to individual patients based on genetic predictors of drug response. The potential role of biomarkers on clinical decision-making is illustrated in Figure 1. In current practice, as many as 95% of patients with newly diagnosed rheumatoid arthritis (RA) begin treatment with methotrexate (MTX), which will be ineffective for short-term and long-term disease control in up to two-thirds of patients.1,2 Patients who fail treatment with MTX due to insufficient response or toxicity typically add or are switched to another disease-modifying antirheumatic drug (DMARD) or biologic agent.1 Patients progress through multiple treatment options before finding the regimen that adequately controls symptoms with acceptable tolerance. The costs and potential safety risks associated with multiple ineffective therapies are high. Personalized medicine aims to refine current treatment algorithms, allowing rheumatologists to select optimal treatments for first-line care. A personalized approach to treatment selection will become important as new biologic therapies enter the therapeutic landscape, presenting even more complex decision-making for clinicians managing patients with rheumatic diseases.

Figure 1. Potential Impact of Biomarkers on Treatment

<table>
<thead>
<tr>
<th>Current Typical Treatment Approach</th>
<th>Future Treatment Approach</th>
</tr>
</thead>
<tbody>
<tr>
<td>“One size fits all” treatment approach based on evidence-based guidelines, insurance, patient preferences, etc.</td>
<td>Baseline biomarker profile</td>
</tr>
<tr>
<td>MTX</td>
<td>Medication 1</td>
</tr>
<tr>
<td>Inadequate response</td>
<td>Medication 2</td>
</tr>
<tr>
<td>Add medication 1</td>
<td>Medication 3</td>
</tr>
<tr>
<td>Inadequate response</td>
<td>Medication 4</td>
</tr>
<tr>
<td>Add medication 2</td>
<td></td>
</tr>
</tbody>
</table>

With noninvasive biomarker assays that predict response or non-response to therapy, rheumatologists will be able to prescribe the right treatment for the right person at the right time. In addition, tests of disease susceptibility and preclinical disease activity will allow clinicians to identify patients who may benefit from increased monitoring and risk-factor reduction. With the development of new biomarker assays, rheumatologists and other healthcare providers (HCPs) must prepare for the growth of personalized medicine in the rheumatology clinic.
According to investigators, the Getting to Your Destination Faster survey findings indicate that patients with RA want to be actively involved in the management of their disease, starting with setting personal treatment goals. This strategy aligns with recent EULAR recommendations, which state that treatment goals for RA should be established early and attained within 3 to 6 months, if possible. If initial treatment goals are not reached within 3 to 6 months, HCPs should consider modifying RA treatment by adding or switching to more potent therapy.

OMERACT
Beginning in 1992 as the Outcome Measures in Rheumatoid Arthritis Clinical Trials (OMERACT) initiative, this international association of clinical and research scientists interested in improving outcome measures in rheumatology has expanded its scope of interest to include most rheumatologic diseases, including psoriatic arthritis (PsA) and spondyloarthritis (SpA). As such, the OMERACT acronym is now more broadly explained as “Outcome Measures in Rheumatology Clinical Trials.”

OMERACT meetings are held every 2 years to develop consensus guidelines that address specific questions in rheumatology, including the use of biomarkers in disease management. The OMERACT Soluble Biomarker special interest group (SIG) published its first draft criteria following the OMERACT 8 workshop in 2006. Two years later, the group published the updated OMERACT 9 draft criteria for determining whether biomarkers can be considered valid markers of structural damage in RA, PsA, and SpA. To be endorsed by OMERACT, a biomarker must successfully pass through the OMERACT Filter, a collection of criteria separated into 3 categories: truth, discrimination, and feasibility. These categories are designed to answer the following critical questions about biomarker performance:

- **Truth:** Does the biomarker truly measure what it intends to measure? Is it clinically relevant?
- **Discrimination:** Does the biomarker discriminate between healthy and affected individuals? Does it differentiate levels of disease severity?
- **Feasibility:** Can the biomarker be measured quickly, easily, inexpensively, and in a way that is easy to interpret? Is it practical for use in everyday clinical practice?

After the 2010 OMERACT 10 meeting, several SIGs have published updated criteria for disease assessment in rheumatology. These include new definitions of disease activity in PsA, ankylosing spondylitis (AS), and gout, as well as the endorsement of serum urate in patients with chronic gout as the first validated soluble biomarker in rheumatology (see Gout, page 11).

TETRAD
The Treatment Efficacy and Toxicity in Rheumatoid Arthritis Database and Repository (TETRAD) is a major initiative designed with the goal of improving the overall level of care for patients with RA, in part through biomarker discovery and validation. The TETRAD collaboration, led by investigative rheumatologists at the University of Alabama at Birmingham, is funded by a multi-year grant from the National Institute of Arthritis and Musculoskeletal and Skin Diseases. Additional research sites include Brigham and Women's Hospital, Duke University Medical Center, Johns Hopkins University, University of California at San Francisco, and other academic medical centers.
How can personalized medicine in rheumatology be best described, and what are some of its benefits and limitations?

Daniel E. Furst, MD: The concept of personalized medicine is, of course, an excellent goal and one that we hope to achieve. In many ways, we see that today’s biomarkers refer to the presence of disease or predict severity of RA, but are less robust when describing RA disease activity. In this arena in particular, it is probable that serum protein markers and examination of gene “signatures” may be more helpful than static gene arrays, as it will be important to seek changes in gene activity or proteins in response to therapy so that treatment can be actually tailored to changing circumstances. Thus, as genes become suppressed or induced, or protein concentrations rise or fall in response to a therapy, changes in treatment may be indicated.

Further developments in the analysis of results may be needed before biomarkers are as useful as we would like them to be. The associations found relate to group data, while the very term “personalized medicine” relates to the individual patient. It is unrealistic to expect any single biomarker to have 100% sensitivity and 100% specificity, so single or grouped biomarkers can, at best, predict probabilities of response rather than certainty of response.

Despite the limitations and associated with the biomarkers of today, clear progress is being made, and we can all expect that practical, useful biomarkers will eventually be available to help us care for patients with RA.

Toward the goal of building a large-scale collaborative registry, TETRAD is currently collecting clinical data and biological specimens—including medication history, radiographic data, and blood samples for DNA, RNA, and serum/plasma analysis—from RA patients who are initiating drug treatment. Ultimately, TETRAD resources may accelerate translational research in RA toward better treatment options and improved patient care by creating a large database and repository, which researchers throughout the world can access to study the molecular pathways of response to different drugs in patients with RA, and ultimately identify predictive biomarkers.

CORRONA CERTAIN Substudy

The Consortium of Rheumatology Researchers of North America (CORRONA) registry includes more than 27,000 RA patients enrolled from private and academic centers throughout the United States. A subset of these patients is also being evaluated in the CORRONA Effectiveness Registry to Study Therapies for Arthritis and Inflammatory Conditions (CERTAIN) project. The study is designed to systematically collect and document usage patterns, effectiveness, and safety of biologic agents in patients with RA. Blood samples are being collected for DNA extraction and mRNA analysis for pharmacogenetic, genomic, proteomic, and other biomarker research.

GRAPPA

The Group for Research and Assessment of Psoriasis and Psoriatic Arthritis (GRAPPA) collaboration is an international consortium promoting advancements in PsA, including the discovery of genes associated with disease susceptibility and therapeutic response. GRAPPA and the soluble biomarker working group of OMERACT have partnered to conduct a long-term study that includes the evaluation of potential biomarkers in PsA. The GRAPPA/OMERACT study will enroll patients with PsA.
Biomarkers in RA

Among the rheumatic diseases, biomarker research in RA has been the most fruitful to date. Dozens of individual biomarkers that provide objective measures of RA susceptibility, disease activity, and therapeutic response have been identified (Table 1). The simultaneous testing of multiple biomarkers in a single assay provides clinicians with a comprehensive snapshot of a complex and heterogeneous disease process. Advances in biomarker research have important implications for RA assessment and management.

Table 1. Biomarkers of RA Development and Progression

<table>
<thead>
<tr>
<th>Biomarker</th>
<th>Source</th>
<th>Outcome</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>AUTOANTIBODIES</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>RF</td>
<td>Blood (serum)</td>
<td>• Disease severity</td>
</tr>
<tr>
<td></td>
<td></td>
<td>• Radiologic progression</td>
</tr>
<tr>
<td>Anti-CCP antibody</td>
<td>Blood (serum)</td>
<td>• Development of RA</td>
</tr>
<tr>
<td></td>
<td></td>
<td>• Severity of RA</td>
</tr>
<tr>
<td><strong>INFLAMMATORY MARKERS</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>ESR</td>
<td>Blood</td>
<td>• Disease activity</td>
</tr>
<tr>
<td></td>
<td></td>
<td>• Radiologic progression</td>
</tr>
<tr>
<td>CRP</td>
<td>Blood (serum)</td>
<td>• Disease activity</td>
</tr>
<tr>
<td></td>
<td></td>
<td>• Radiologic progression</td>
</tr>
<tr>
<td>Cytokines</td>
<td>Blood (serum), synovial fluid,</td>
<td>• Disease activity</td>
</tr>
<tr>
<td></td>
<td>synovial membrane</td>
<td>• Inflammation</td>
</tr>
<tr>
<td></td>
<td></td>
<td>• Radiologic progression</td>
</tr>
<tr>
<td><strong>IMMUNOLOGIC MARKER</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>T cells</td>
<td>Blood, synovial fluid</td>
<td>• Disease development</td>
</tr>
<tr>
<td></td>
<td></td>
<td>• Disease activity</td>
</tr>
<tr>
<td><strong>MARKERS OF JOINT DESTRUCTION</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>CTX-II</td>
<td>Urine</td>
<td>• Cartilage destruction</td>
</tr>
<tr>
<td></td>
<td></td>
<td>• Radiographic progression</td>
</tr>
<tr>
<td>MMPs</td>
<td>Blood (serum)</td>
<td>• Disease activity</td>
</tr>
<tr>
<td></td>
<td></td>
<td>• Radiologic progression</td>
</tr>
<tr>
<td>ADAMTS5</td>
<td>Blood (serum)</td>
<td>• Therapeutic response</td>
</tr>
<tr>
<td>RANKL</td>
<td>Blood (serum), synovial fluid</td>
<td>• Bone destruction</td>
</tr>
<tr>
<td><strong>GENETIC MARKERS</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>HLA-DRB1</td>
<td>Blood (DNA)</td>
<td>• Development of RA</td>
</tr>
<tr>
<td></td>
<td></td>
<td>• ACPA seropositivity</td>
</tr>
<tr>
<td>PTPN22</td>
<td>Blood (DNA)</td>
<td>• Development of RA</td>
</tr>
<tr>
<td></td>
<td></td>
<td>• ACPA seropositivity</td>
</tr>
<tr>
<td>TNF-308G A/G polymorphism</td>
<td>Blood (DNA)</td>
<td>• Response to anti-TNF therapy</td>
</tr>
<tr>
<td><strong>DRUG METABOLITES AND ANTIDRUG ANTIBODIES</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>MTX polyglutamates</td>
<td>Blood (RBCs)</td>
<td>• Response to MTX therapy</td>
</tr>
<tr>
<td>Antidrug antibodies</td>
<td>Blood (serum)</td>
<td>• Response to anti-TNF therapy</td>
</tr>
</tbody>
</table>

ACPA=anti-citrullinated protein antibody; ADAMTS5=disintegrin and metalloproteinase with thrombospondin motifs 5; CCP=cyclic citrullinated peptide; CRP=C-reactive protein; CTX-C-terminal crosslinked telopeptide of type II collagen; ESR=erythrocyte sedimentation rate; HLA-DRB1=human leukocyte antigen with DRB allele; MMP=matrix metalloproteinase; PTPN22=protein tyrosine phosphatase, non-receptor type 22; RANKL=receptor activator for nuclear factor kappa-B ligand; RBC=red blood cell; RF=rheumatoid factor; TNF=tumor necrosis factor
RF and anti-CCP antibodies may have an emerging role in predicting treatment response to conventional and biologic DMARDs. In a pooled analysis of 2 phase III studies, baseline RF and anti-CCP status significantly correlated with response to treatment with rituximab and MTX in 670 patients with RA. Patients who were seropositive at baseline—defined as RF >20 international units/mL and/or anti-CCP >5 units/mL—were more likely than seronegative patients to respond after 24 weeks of treatment. After 48 weeks, seropositive patients were 3 times more likely to achieve remission than seronegative patients (OR, 3.3; 95% CI, 1.40-7.82). In another phase III study, autoantibody levels predicted response to rituximab in patients with active RA who failed prior anti-tumor necrosis factor (anti-TNF) therapy. Patients who were seropositive for RF and/or anti-CCP at baseline were significantly more likely to achieve a EULAR response at 24 weeks (OR, 3.5; 95% CI, 1.6-7.6). The likelihood of achieving a response was even higher for patients with baseline autoantibodies and elevated serum IgG levels (OR, 6.0; 95% CI, 2.2-16.2). The concentration and behavior of acute-phase reactants are routinely available and are easy to perform, making ESR and CRP the most widely used biomarkers for assessing disease activity in RA. As part of the American College of Rheumatology’s 20% improvement criteria (ACR20), acute-phase reactants have been identified as the most commonly used biomarkers in the assessment of RA treatment response.

Inflammatory markers also predict response to treatment with anti-TNF therapy. Type I interferon (IFN) is a pleiotropic cytokine associated with diverse immunomodulatory effects. In patients with RA, IFN-beta appears to serve a protective role by reducing the expression of TNF- and interleukin (IL)-1 and enhancing the activity of anti-inflammatory cytokines, including IL-1 receptor antagonist (IL-1Ra). In a study of patients with RA, high baseline plasma IFN activity (OR, 1.36; P=0.020) and high baseline IL-1Ra levels (OR, 1.82; P=0.027) significantly correlated with better responses to anti-TNF therapy.

**Immunologic Markers**

The concentration and behavior of lymphocytes, including T cells and B cells, provide important information about inflammatory activity and treatment response in patients with RA. Post-infusion B-cell concentrations predict response to rituximab and elevated levels of activated T cells predict relapse in patients with RA in clinical remission.

In preliminary studies, T-cell expression of CD91 appears to differentiate responders and non-responders to anti-TNF therapy. In a study of patients with early RA who were initiating treatment with TNF inhibitors, non-responders had significantly higher levels of CD91 expression on CD3-positive T cells at 6 weeks than responders (P=0.05). By comparison, expression levels of other T cell surface proteins, including thrombospondin-1, calreticulin, and CD47, did not differ between non-responders and responders. Thus, preliminary evidence suggests that T-cell expression of CD91 appears to be a specific marker

**Autoantibodies**

As signature features of RA and other rheumatic diseases, autoantibodies have become important diagnostic tools and predictors of increased disease severity. Rheumatoid factor (RF) is a non-specific marker of RA that is present in up to 80% of RA patients. The presence of RF is associated with increased levels of disease activity and bone erosion early in the course of RA, but becomes less predictive as disease progresses. Therefore, the value of RF as a diagnostic marker depends on disease stage. Compared with RF, anti-cyclic citrullinated peptide (anti-CCP) antibodies are more specific for RA, providing better utility as a diagnostic marker. Anti-CCP antibodies are also associated with greater disease activity and faster radiologic progression, even with the administration of aggressive therapy. In patients with RA, the presence of anti-CCP antibodies suggests a poorer prognosis and, in combination with high disease activity or radiographic damage, highlights the need for early therapy with biologic DMARDs.

**Immunologic Markers**

The concentration and behavior of lymphocytes, including T cells and B cells, provide important information about inflammatory activity and treatment response in patients with RA. Post-infusion B-cell concentrations predict response to rituximab and elevated levels of activated T cells predict relapse in patients with RA in clinical remission.

In preliminary studies, T-cell expression of CD91 appears to differentiate responders and non-responders to anti-TNF therapy. In a study of patients with early RA who were initiating treatment with TNF inhibitors, non-responders had significantly higher levels of CD91 expression on CD3-positive T cells at 6 weeks than responders (P=0.05). By comparison, expression levels of other T cell surface proteins, including thrombospondin-1, calreticulin, and CD47, did not differ between non-responders and responders. Thus, preliminary evidence suggests that T-cell expression of CD91 appears to be a specific marker of...
unresponsiveness to anti-TNF therapy in patients with RA, but these findings need to be corroborated in additional studies.

**Biomarkers of Joint Destruction**

Biomarkers that reflect turnover in the synovium, cartilage, and bone may be useful for monitoring disease activity and predicting treatment response in patients with RA. Biomarkers in this family include the **matrix metalloproteinases (MMPs)**, which are enzymes involved in articular cartilage degradation; **urinary C-terminal crosslinked telopeptide of type I and II collagen (CTX-I and CTX-II)**, which are markers of collagen breakdown; and **receptor activator for nuclear factor kappa-B ligand (RANKL)**, a marker of bone degradation. The phase II Synovial Pannus Evaluation and Cytokine-Targeted Therapy in Rheumatoid Arthritis (SPECTRA) trial evaluated 22 biomarkers as potential indicators of disease activity, treatment response, and radiographic progression. Among the markers of joint damage, MMP-1, MMP-3, and **tissue inhibitor of metalloproteinase 1 (TIMP-1)** showed the most promise. Both MMP-1 and TIMP-1 were significantly associated with radiographic progression, and early TIMP-1 activity following treatment initiation predicted later therapeutic outcome.

**Genetic Markers**

Approximately 60% of the risk of developing RA is attributable to genetic factors. With advances in technology, substantial progress has been made in understanding the genetic basis for variations in RA risk and therapeutic response. Single nucleotide polymorphisms (SNPs) are variations in DNA sequences in which one nucleotide varies among individuals. SNPs account for approximately 80% of all known polymorphisms and can be associated with disease risk, gene-environment interactions, and drug metabolism. Genome-wide association (GWA) studies scan hundreds of thousands of SNPs to identify genetic regions that

---

**What does new or emerging information tell us about biomarkers in RA? How might this affect personalized medicine?**

S. Louis Bridges, Jr., MD, PhD: Biomarkers of treatment response in RA may provide important insight into molecular subphenotypes of disease. For example, patients in which T cells play an important role in the pathogenesis of RA may preferentially benefit from treatment with abatacept, while those with a B-cell dominant phenotype may have excellent clinical responses to rituximab. Similar biomarkers of the predominance of the TNF or IL-6 pathways in RA may point to TNF inhibitors or tocilizumab as optimal treatments for individual patients.

Because of the expense and potential side effects of biologic agents used to treat RA, biomarkers of treatment response are of interest to physicians, patients, and insurers. Results of studies investigating genetic polymorphisms underlying treatment responses or adverse events to DMARDs or biologic agents have been disappointing to date. Analyses of serum proteins, biochemical markers, and gene expression in peripheral blood cells may ultimately identify markers of treatment response that may be used to stratify patients.

Among the obstacles to personalized medicine in RA is the lack of large databases with prospectively collected treatment outcome data and corresponding biological samples such as serum, cells, or RNA for proteomic, cellular, or gene expression studies, respectively. When large datasets on well-phenotyped patients become available, the goals of personalized medicine will be greatly advanced.
are associated with disease susceptibility, severity, or other phenotypic characteristics, such as therapeutic response to particular medications.

The human leukocyte antigen (HLA)-DRB1 allele is a major genetic risk factor for RA. The HLA-DRB1 alleles encoding the shared epitope (SE) account for approximately 40% of the genetic risk of RA. Another susceptibility gene, the protein tyrosine phosphatase, non-receptor type 22 (PTPN22) gene, has an attributable risk fraction of approximately 8% in populations of Northern European ancestry. Certain gene-environment interactions can dramatically influence the magnitude of RA risk. For instance, smoking only modestly increases RA risk in patients who do not harbor HLA-DRB1 SE alleles. However, in patients with 1 or 2 copies of the HLA-DRB1 SE allele, smoking increases the risk of RA by 6.5-fold and 21-fold, respectively. Conversely, smoking shows little interaction with PTPN22-associated RA risk.

Potential markers of response to biologic therapy include polymorphisms in genes known to be involved in RA pathogenesis, metabolism, and clinical activity. The TNF-308G A/G polymorphism has emerged as a potential predictor of response to anti-TNF treatment. In several studies of patients with RA undergoing treatment with TNF inhibitors, those who carried the A allele had a poorer response to treatment than those with the G allele. This finding has not been replicated in all studies of TNF inhibitors in RA, including in GWA studies of anti-TNF response in patients with RA. The -174 C/G polymorphism of the IL-6 gene significantly influences IL-6 production in response to inflammatory stimuli, and preliminary evidence shows that it appears to influence response to anti-IL-6 therapy. The C allele, which is present in approximately 40% of individuals, is associated with significantly lower levels of plasma IL-6 and poorer responses to IL-6 inhibitor treatment.

Drug Metabolites and Antidrug Antibodies
Approximately 30% of patients with RA discontinue MTX treatment within 2 years due to side effects or inadequate efficacy. As a prodrug, MTX requires enzymatic conversion to MTX polyglutamates (MTXPGs) to exert anti-inflammatory activity within the joints. Some patients with RA harbor certain SNPs that interfere with MTX metabolism and clinical activity. Measuring MTXPG metabolites may allow clinicians to determine whether partial or nonresponders to MTX might benefit from continued dose escalation or require a change in therapy.

During treatment with a biologic DMARD, the development of antidrug antibodies predicts antibody-related adverse events and treatment failure. In a study of patients with RA who were treated with adalimumab, 28% of patients developed antidrug antibodies, mostly within the first 28 weeks of treatment. Patients who developed antidrug antibodies were 3 times more likely than those without antibodies to stop taking adalimumab due to treatment failure and significantly less likely to achieve a sustained remission. In another study, the development of antidrug antibodies to first-line anti-TNF therapy predicted a better response to subsequent second-line biologic therapy. Monitoring patients for the production of antidrug antibodies, particularly in the early months of treatment, may identify those with an increased risk of inadequate treatment response. Such patients may benefit from switching to a different biologic DMARD.

Use of Multi-Biomarker Disease Activity Panels
Assays that integrate information from multiple biomarkers have the potential to provide a comprehensive snapshot of disease activity in patients with RA. One multi-biomarker disease activity (MBDA) assay for measuring and monitoring disease activity in RA was developed by screening approximately 400 candidate biomarkers to identify the strongest predictors of clinical disease activity across a range of patients with RA. The MBDA assay compiles information from 12 biomarkers—each independently validated to reflect disease activity in RA—into a single quantitative score. The MBDA score ranges from 1 to 100, with defined thresholds for low (1-28), moderate (29-43), and high (>44) disease activity. Biomarkers included in the MBDA assay are summarized in Table 2.

Table 2. Components of the MBDA Assay

<table>
<thead>
<tr>
<th>Acute-phase proteins</th>
<th>• CRP</th>
<th>• SAA</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cytokines and related protein</td>
<td>• IL-6</td>
<td>• TNF-R</td>
</tr>
<tr>
<td>Adhesion molecule MMPs</td>
<td>• VCAM-1</td>
<td>• MMP-1, or collagenase-1</td>
</tr>
<tr>
<td>• MMP-3, orstromelysin-1</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Skeletal-related protein</td>
<td>• YKL-40, or human cartilage glycoprotein-39</td>
<td></td>
</tr>
<tr>
<td>Growth factors</td>
<td>• EGF</td>
<td>• VEGF-A</td>
</tr>
<tr>
<td>Hormones</td>
<td>• Lactin</td>
<td>• Resistin</td>
</tr>
</tbody>
</table>

101 - PERSONALIZED MEDICINE IN RHEUMATOLOGY: TOMORROW’S PROMISE OR TODAY’S REALITY
Gout

Although gout is often managed at the primary care level, it provides an important example of recent progress toward personalized medicine in the rheumatology setting. According to reports from OMERACT 10, serum urate (SU) in chronic gout may become the first candidate biomarker to fulfill the OMERACT Filter as a validated biomarker in rheumatology. The majority of OMERACT 10 participants (78%) agreed that SU meets the OMERACT Filter for feasibility, truth, and discrimination in the following ways10:

- **Truth**: The SU assay results are generally reproducible, with between-laboratory and between-method coefficients of variation of <5%. The sources of potential variability of SU measurements, including age, gender, ethnicity, and body mass index as well as cardiac, renal, and hepatic function are well documented.

- **Discrimination**: SU is independently associated with clinical and patient-centered endpoints in chronic gout, including flare frequency, pain, patient global assessment, disability, and health-related quality of life.

- **Feasibility**: An internationally standardized assay for SU is widely available for use in clinical practice. Once collected, SU is stable in serum for an acceptable duration at room temperature (48 hours), refrigerated (8 days), or frozen (4 months) and is not adversely affected by repeat freeze-thaw cycles.

Despite agreement on these points, OMERACT 10 participants did not reach a consensus about whether SU should be endorsed as a validated biomarker. Some important questions remained, particularly regarding the role of SU in predicting tophus regression, dissolution of crystals, and radiographic damage in patients with chronic gout. The final vote was split, with approximately one-third of participants agreeing (34%), disagreeing (32%), or expressing uncertainty (34%) about endorsing SU. According to Stamp et al, OMERACT approval of SU as the first validated soluble biomarker in rheumatology is close and may be realized by web-based voting prior to OMERACT 11.11

**Biomarkers in Other Rheumatic Diseases**

In addition to advances in RA, promising results are also emerging from biomarker studies of patients with gout, PsA, AS, and systemic lupus erythematosus (SLE). In the future, the use of genetic and molecular biomarkers of disease susceptibility, prognosis, and treatment response may become a standard tool for patient management in the rheumatology clinic.

**HLA-B*5801**

Patients with gout who carry the HLA-B*5801 allele have an increased risk for severe cutaneous adverse reactions to treatment with allopurinol, a drug commonly used to lower uric acid in the treatment of gouty arthritis. HLA-B*5801-associated allopurinol hypersensitivity has been identified in patients of Asian ancestry, including Han Chinese and Thai populations.55,56 As a genetic marker for adverse events, HLA-B*5801 screening may be appropriate for specific patient populations at risk for allopurinol-induced Stevens-Johnson syndrome or toxic epidermal necrolysis.
DIAGNOSTIC MARKERS

 Few diagnostic biomarkers for PsA have been identified to date. Traditional acute-phase reactants are elevated in only 50% of patients with active PsA, and serum levels do not predict therapeutic response.59 Newer biomarkers show promise for differentiating between PsA patients and those with psoriasis who do not have arthritis. For instance, Chandran et al recently identified 4 soluble biomarkers—high-sensitivity CRP (hsCRP), osteoprotegerin (OPG), MMP-3, and the C-propeptide of type II collagen: collagen fragment neoepitopes Col2-3/4long mono ratio (CPII:C2C)—that independently predict PsA in patients with psoriasis.62

MARKERS OF TREATMENT RESPONSE

Personalized medicine in the area of PsA has been limited by the lack of biomarkers for disease severity and therapeutic response. However, progress is being made in this area. The OMERACT Filter requires candidate biomarkers to serve as proxies of validated outcomes, and, to date, there has been little consensus regarding optimal measures of disease activity in PsA. At the OMERACT 10 meeting, members of the PsA SIG evaluated a newly proposed algorithm for measuring disease severity and treatment response in PsA.7 Developed in conjunction with the GRAPPA Composite Exercise (GRACE) study, the Composite Psoriatic Disease Activity Index (CPDAI) reflects disease activity in several domains of psoriatic disease. The CPDAI assigns a score of 0 to 3 to each of the 5 domains of PsA, resulting in a total score of 0 to 15 (Table 3). To fulfill the OMERACT Filter, future candidate biomarkers of PsA disease severity and therapeutic response may need to demonstrate correlation with the CPDAI. This proposed CPDAI composite measure is being further refined in ongoing analyses of the GRACE study, and alternative candidate composite measures of disease activity and treatment response will be proposed at the OMERACT 11 meeting.

SUSCEPTIBILITY MARKERS

The search for a robust biomarker of PsA risk is still underway. Several genes associated with the major histocompatibility complex (MHC) correlate with PsA, but each contributes only modestly to the total genetic risk of PsA. The HLA-C*06 allele is associated with a 5-fold risk in the development of PsA in patients with type I psoriasis, but shows no link with PsA among those with type II psoriasis.60 Recently, Boudreau et al described the correlation between the HLA-complex P5 (HCP5) gene and PsA. The correlation between PsA and rs2395029, an SNP located within Exon 2 of the HCP5 gene, was independent of any associations with nearby HLA genes, including HLA-C, HLA-B, or MICA.61

Psoriatic Arthritis

PsA is a chronic form of inflammatory arthritis that affects up to 25% of patients with psoriasis.57 As a result of widespread underdiagnosis, PsA is often associated with delayed treatment, loss of function, and poor quality of life.58,59

<table>
<thead>
<tr>
<th>Table 3. CPDAI Scoring</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>PsA Domain</strong></td>
</tr>
<tr>
<td></td>
</tr>
<tr>
<td>Peripheral arthritis</td>
</tr>
<tr>
<td>Skin disease</td>
</tr>
<tr>
<td>Enthesitis</td>
</tr>
<tr>
<td>Dactylitis</td>
</tr>
<tr>
<td>Spinal disease</td>
</tr>
</tbody>
</table>

*HAQ only counted if clinical involvement of domain (joint/enthesis/dactylitis) present. ASQoL=Ankylosing Spondylitis Quality of Life Index; BASDAI=Bath Ankylosing Spondylitis Disease Activity Index; DLQI=Dermatology Life Quality Index; HAQ=Health Assessment Questionnaire; PASI=Psoriasis Activity and Severity Index.

PsA is a chronic form of inflammatory arthritis that affects up to 25% of patients with psoriasis.57 As a result of widespread underdiagnosis, PsA is often associated with delayed treatment, loss of function, and poor quality of life.58,59

SUSCEPTIBILITY MARKERS

The search for a robust biomarker of PsA risk is still underway. Several genes associated with the major histocompatibility complex (MHC) correlate with PsA, but each contributes only modestly to the total genetic risk of PsA. The HLA-C*06 allele is associated with a 5-fold risk in the development of PsA in patients with type I psoriasis, but shows no link with PsA among those with type II psoriasis.60 Recently, Boudreau et al described the correlation between the HLA-complex P5 (HCP5) gene and PsA. The correlation between PsA and rs2395029, an SNP located within Exon 2 of the HCP5 gene, was independent of any associations with nearby HLA genes, including HLA-C, HLA-B, or MICA.61

Psoriatic Arthritis

PsA is a chronic form of inflammatory arthritis that affects up to 25% of patients with psoriasis.57 As a result of widespread underdiagnosis, PsA is often associated with delayed treatment, loss of function, and poor quality of life.58,59

SUSCEPTIBILITY MARKERS

The search for a robust biomarker of PsA risk is still underway. Several genes associated with the major histocompatibility complex (MHC) correlate with PsA, but each contributes only modestly to the total genetic risk of PsA. The HLA-C*06 allele is associated with a 5-fold risk in the development of PsA in patients with type I psoriasis, but shows no link with PsA among those with type II psoriasis.60 Recently, Boudreau et al described the correlation between the HLA-complex P5 (HCP5) gene and PsA. The correlation between PsA and rs2395029, an SNP located within Exon 2 of the HCP5 gene, was independent of any associations with nearby HLA genes, including HLA-C, HLA-B, or MICA.61

Psoriatic Arthritis

PsA is a chronic form of inflammatory arthritis that affects up to 25% of patients with psoriasis.57 As a result of widespread underdiagnosis, PsA is often associated with delayed treatment, loss of function, and poor quality of life.58,59

SUSCEPTIBILITY MARKERS

The search for a robust biomarker of PsA risk is still underway. Several genes associated with the major histocompatibility complex (MHC) correlate with PsA, but each contributes only modestly to the total genetic risk of PsA. The HLA-C*06 allele is associated with a 5-fold risk in the development of PsA in patients with type I psoriasis, but shows no link with PsA among those with type II psoriasis.60 Recently, Boudreau et al described the correlation between the HLA-complex P5 (HCP5) gene and PsA. The correlation between PsA and rs2395029, an SNP located within Exon 2 of the HCP5 gene, was independent of any associations with nearby HLA genes, including HLA-C, HLA-B, or MICA.61

Psoriatic Arthritis

PsA is a chronic form of inflammatory arthritis that affects up to 25% of patients with psoriasis.57 As a result of widespread underdiagnosis, PsA is often associated with delayed treatment, loss of function, and poor quality of life.58,59

SUSCEPTIBILITY MARKERS

The search for a robust biomarker of PsA risk is still underway. Several genes associated with the major histocompatibility complex (MHC) correlate with PsA, but each contributes only modestly to the total genetic risk of PsA. The HLA-C*06 allele is associated with a 5-fold risk in the development of PsA in patients with type I psoriasis, but shows no link with PsA among those with type II psoriasis.60 Recently, Boudreau et al described the correlation between the HLA-complex P5 (HCP5) gene and PsA. The correlation between PsA and rs2395029, an SNP located within Exon 2 of the HCP5 gene, was independent of any associations with nearby HLA genes, including HLA-C, HLA-B, or MICA.61

Psoriatic Arthritis

PsA is a chronic form of inflammatory arthritis that affects up to 25% of patients with psoriasis.57 As a result of widespread underdiagnosis, PsA is often associated with delayed treatment, loss of function, and poor quality of life.58,59

SUSCEPTIBILITY MARKERS

The search for a robust biomarker of PsA risk is still underway. Several genes associated with the major histocompatibility complex (MHC) correlate with PsA, but each contributes only modestly to the total genetic risk of PsA. The HLA-C*06 allele is associated with a 5-fold risk in the development of PsA in patients with type I psoriasis, but shows no link with PsA among those with type II psoriasis.60 Recently, Boudreau et al described the correlation between the HLA-complex P5 (HCP5) gene and PsA. The correlation between PsA and rs2395029, an SNP located within Exon 2 of the HCP5 gene, was independent of any associations with nearby HLA genes, including HLA-C, HLA-B, or MICA.61

Psoriatic Arthritis

PsA is a chronic form of inflammatory arthritis that affects up to 25% of patients with psoriasis.57 As a result of widespread underdiagnosis, PsA is often associated with delayed treatment, loss of function, and poor quality of life.58,59

SUSCEPTIBILITY MARKERS

The search for a robust biomarker of PsA risk is still underway. Several genes associated with the major histocompatibility complex (MHC) correlate with PsA, but each contributes only modestly to the total genetic risk of PsA. The HLA-C*06 allele is associated with a 5-fold risk in the development of PsA in patients with type I psoriasis, but shows no link with PsA among those with type II psoriasis.60 Recently, Boudreau et al described the correlation between the HLA-complex P5 (HCP5) gene and PsA. The correlation between PsA and rs2395029, an SNP located within Exon 2 of the HCP5 gene, was independent of any associations with nearby HLA genes, including HLA-C, HLA-B, or MICA.61

Psoriatic Arthritis

PsA is a chronic form of inflammatory arthritis that affects up to 25% of patients with psoriasis.57 As a result of widespread underdiagnosis, PsA is often associated with delayed treatment, loss of function, and poor quality of life.58,59

SUSCEPTIBILITY MARKERS

The search for a robust biomarker of PsA risk is still underway. Several genes associated with the major histocompatibility complex (MHC) correlate with PsA, but each contributes only modestly to the total genetic risk of PsA. The HLA-C*06 allele is associated with a 5-fold risk in the development of PsA in patients with type I psoriasis, but shows no link with PsA among those with type II psoriasis.60 Recently, Boudreau et al described the correlation between the HLA-complex P5 (HCP5) gene and PsA. The correlation between PsA and rs2395029, an SNP located within Exon 2 of the HCP5 gene, was independent of any associations with nearby HLA genes, including HLA-C, HLA-B, or MICA.61
Ankylosing Spondylitis

AS is a debilitating and frequently misdiagnosed spondyloarthropathy that can cause significant disability and impairment in quality of life. AS is a highly heritable disease, with more than 90% of AS risk attributable to genetic factors. In recent years, considerable progress has been made in identifying additional genes associated with AS susceptibility.

Susceptibility and Diagnostic Markers

Genes within or near the MHC are especially prominent in studies of AS risk. Variations in the HLA-B27 immune response gene account for more than one-third (37%) of the genetic susceptibility to AS. In a study of HLA-B27-positive individuals with or without AS, several additional HLA markers were also associated with AS, particularly the HLA-DPA1*01:03, HLA-DPA1*02:01, and HLA-DPB1*13:01 subtypes. Using GWA studies, researchers are able to identify multiple non-MHC genes associated with AS risk. Pimentel-Santos et al identified a 14-gene expression signature of AS susceptibility, including several genes known to be involved in systemic inflammation (PTPN1, DOCK10) or bone and cartilage metabolism (SPOCK2, EP300). In a large meta-analysis of biomarker discovery and validation, the histone demethylase gene JARID1A was strongly associated with AS. Several variants of immune-related genes such as ERAP1, IL-23R, IL-1, and ORA1 also confer susceptibility to AS. Gene-gene interactions, such as between ERAP1 polymorphisms and HLA-B27, also influence AS risk.

Markers of Treatment Response

Several potential markers correlate with therapeutic response in patients with AS who are undergoing treatment with conventional or biologic DMARDs. Patients who were younger (<40 years; P<0.0001), had fewer swollen joints (<3; P<0.0001), or had fewer years of pain and stiffness (<5 years; P=0.0053) were most likely to respond to treatment with either sulfasalazine (SSZ) or etanercept. Higher responses were also seen in HLA-B27-positive patients and those with lower baseline indicators of disease activity, including CRP no higher than the upper limit of normal (P=0.0019), Bath Ankylosing Spondylitis Metrology Index (BASMI) ≤3 (P=0.0023), or Bath Ankylosing Spondylitis Functional Index (BASFI) ≤5 (P=0.0028). Younger age was the only marker that predicted better response to etanercept than to SSZ. Clinical, molecular, and genetic markers of response to anti-TNF therapy were also evaluated in a combined analysis of the Ankylosing Spondylitis Study for the Evaluation of Recombinant Infliximab Therapy (ASSERT) and Golimumab-A Randomized Study in Ankylosing Spondylitis Subjects of a Novel Anti-TNF mAB Injection Given Every Four Weeks (GO-RAISE) trials. A prediction model that incorporated data on patient age, enthesitis score, serum CRP level, BASFI score, and HLA-B27 status correctly predicted the probability of achieving a response to TNF inhibitor therapy. In another study of patients with AS who were treated with anti-TNF therapy for 48 weeks, baseline and on-treatment levels of vascular endothelial growth factor (VEGF) and CTX-II levels were able to distinguish responders and non-responders defined by Bath Ankylosing Spondylitis Disease Activity Index (BASDAI) scores. By comparison, CRP, IL-6, VEGF, aggrecan, and osteocalcin were associated with treatment response, as measured by the AS Disease Activity Score (ASDAS). At the OMERACT 10 meeting, the AS SIG endorsed the ASDAS as a validated outcome measure ready for use in clinical practice and research settings.
Systemic Lupus Erythematosus

SLE is a chronic inflammatory disease marked by clinical flares and an increased risk for cardiovascular and renal disease. Genetic studies have identified genetic loci associated with SLE susceptibility and clinical heterogeneity. In one study, several genes were significantly associated with renal disease (ITGAM, TNFSF4), hematologic disorder (IL-21), malar rash (FCGR2A), discoid rash (ITGAM), and protection from oral ulcers (STAT4) in patients with SLE.78

Microarray technology can provide clinically valuable prognostic information, as demonstrated by the MammaPrint™ 70-gene expression signature for predicting outcomes in breast cancer patients. In a meta-analysis of DNA microarray datasets, Arasappan et al recently described a 37-gene expression signature for SLE.79 The SLE metasignature includes multiple genes involved in biological pathways that are active in SLE pathogenesis, including IFN signaling, inflammatory and immune response, and cell proliferation and differentiation (Table 4). In an independent dataset, the metasignature clearly differentiated between patients with SLE from healthy individuals. According to study authors, the SLE metasignature may have a future role in the diagnosis and monitoring of patients with SLE.79

Early markers of cardiovascular disease may enable rheumatologists to identify patients with SLE who require intensive monitoring and risk-factor modification. In a study of 250 women with SLE, high serum leptin levels (≥29.5 ng/mL) were associated with an increased risk of atherosclerosis (OR, 2.8; P=0.03).80 In another study of 61 patients with longstanding SLE (median duration, 11.2 years), 36% had echocardiographic abnormalities.81 In a multivariate analysis, every 10-year increase in patient age was associated with a 3.2-fold increased risk of cardiac function abnormalities (P=0.001), and the presence of serositis increased the risk of
electrocardiographic abnormalities by 6.5-fold (P=0.016).\textsuperscript{81} Another study compared the use of 2 common scoring systems, Framingham risk score (FRS) or Systematic Coronary Risk Evaluation (SCORE) risk chart, for evaluating ischemic heart disease (IHD) in patients with SLE.\textsuperscript{82} Patients with SLE and concomitant IHD had a higher FRS (3.33 and 1.15; P=0.001) and higher SCORE risk (1.67 and 0.46; P=0.003) than those with no history of IHD. With a higher area under the curve (0.819 and 0.716), the SCORE system was superior to the FRS in identifying IHD.\textsuperscript{82}

Table 4. SLE Metasignature Genes and Their Functions\textsuperscript{79}

<table>
<thead>
<tr>
<th>Gene Function</th>
<th>Metasignature Genes</th>
</tr>
</thead>
<tbody>
<tr>
<td>IFN signaling and IFN-induced or IFN-regulated genes</td>
<td>IFIT1, IFIT3, IFITM1, MX1, OAS1, STAT1, STAT2, CCL2, CCL5, 1, SOCS1, SOCS3</td>
</tr>
<tr>
<td>Inflammatory and immune response</td>
<td>CCL3, CCR1, CCL5, FCGR1A, ILR2, IL1B, IL1F5, IL-6, IL5, IL15, TRAB, MAP293, MAP296, SAMAD, FCGR2A, FCGR2B, NFKBBA</td>
</tr>
<tr>
<td>Cell proliferation and differentiation</td>
<td>CDK1A, CDK1C, DUSP1, EP300, FOS, JUN, PTAK1, PRKACB</td>
</tr>
<tr>
<td>Protein folding</td>
<td>SLP1</td>
</tr>
</tbody>
</table>

Summary

Rheumatic disorders are heterogeneous diseases with diverse clinical manifestations and underlying phenotypes. Rheumatologists have been using biomarkers such as autoantibodies and acute-phase reactants to predict outcomes and guide clinical decisions for years. New biomarkers can further enhance diagnostic accuracy, assessment of disease severity and prognosis, detection of disease flare, and prediction of treatment response. Ongoing efforts by OMERACT, TETRAD, CORRONA, GRAPPA, and other international collaborations will ensure that new biomarkers meet stringent criteria before being adopted for widespread clinical use. With the availability of new biomarkers and multiple-biomarker assays, rheumatologists may soon be able to select individualized treatment options that are most likely to result in better clinical outcomes.

Instructions on How to Receive Credit

Participants must review the materials on accreditation information, target audience, learning objectives, and disclosure information.

Then Earn CME Credit Online in Three Easy Steps!

To earn up to 0.75 AMA Category 1 Credits\textsuperscript{14} follow these three easy steps:

1. Go to www.pmrheum.com
2. Follow the on-screen instructions to access the post-test and evaluation
3. After passing the post-test, print out your electronic CME certificate

In order to successfully complete this activity for AMA PRA Category 1 Credit\textsuperscript{14}, learners must achieve a minimum of 80% on the post-test.
References


