The potential impact of monitoring disease activity biomarkers on rheumatoid arthritis outcomes and costs

Gary M Oderda^{*1}, Grant D Lawless², Grace C Wright³, Samuel R Nussbaum⁴, Renwyck Elder⁵, Kibum Kim¹ & Diana I Brixner¹

¹University of Utah College of Pharmacy, Salt Lake City, UT 84112, USA

²University of Southern California School of Medicine, Los Angeles, CA 90033, USA

³NYU School of Medicine, New York, NY 10016, USA

⁴University of Southern California, Schaeffer Center for Health Policy and Economics, Los Angeles, CA 90089, USA

⁵AffectRX LLC, Southlake, TX 76092, USA

*Author for correspondence: gary.oderda@pharm.utah.edu

Rheumatoid arthritis (RA) management requires monitoring of disease activity to determine course of treatment. Global assessments are used in clinical practice to determine RA disease activity. Monitoring disease activity via biomarkers may also help providers optimize biologic and nonbiologic drug use while decreasing overall drug spend by delaying use of expensive biologic therapies. By testing multiple biologic domains at the same time, a multibiomarker disease activity test may have utility in RA patient management, through improved intra- and inter-rater reliability. This report provides a comprehensive review of studies of objective measures, single biomarkers and multibiomarker disease activity tests as disease activity measures to decrease uncertainty in treatment decisions, and of biomarkers' potential impact on economic and clinical outcomes of treatment choices.

First draft submitted: 1 January 2018; Accepted for publication: 9 April 2018; Published online: 25 April 2018

Keywords: biomarkers • MBDA • outcomes • personalized medicine • rheumatoid arthritis • targeted therapy

Rheumatoid arthritis (RA) is a chronic, progressive and frequently disabling autoimmune disease that results in joint inflammation and pain and can lead to premature death and disability. RA affects approximately 0.6% of the US adult population (1.5 million people) [1]. RA is three-times more common in women than in men and can begin at any age [2]. Patients' physical and mental health is correlated with pain, loss of function, loss of work participation and decreased quality of life.

From a societal perspective, both direct and indirect costs (primarily loss of productivity from disability and absenteeism) due to RA are substantial. A US observational study showed that at a median of 12.8 years after RA onset, 43.8% of patients who had a job at the time of diagnosis were no longer employed. A fourth to a half of all patients with RA become unable to work within 10–20 years of diagnosis [3]. A recent study tracking the persistence of employees with RA showed that 62% were still actively employed at 4 years while only 35% were still working at 8 years [4], with a median age of disease onset during prime working years at 45 for females and 50 for males [3]. The estimated total cost attributable to RA and other rheumatic conditions in the USA is \$128 billion, with the majority, \$81 billion, from direct medical expenses and \$47 billion from indirect costs [5]. Approximately 44% of RA patients have problems paying medical and drug bills after insurance payments, and 9% report they are unable to purchase all the medications or care they need because of substantial out-of-pocket medical expenses [3]. RA represents a significant burden to society because of its high medical costs and prevalence, and optimized treatment strategies are warranted.

Biomarkers have the potential to improve medical and pharmacy payer policies across therapeutic applications ranging from CNS and cardiovascular disorders to immune system and inflammatory diseases [6]. A quantitative assessment using objective measures and subgroup discrimination has improved reliability while reducing subjective interpretations by clinicians, and has demonstrated clinical utility. Objective measures can potentially improve

Table 1. Summary of traditional disease activity assessment recommended by American College of Rheumatology.

Variables or domains		Disease activity cut-offs			
		Remission	Low	Moderate	High
DAS-28-ESR	TJC, SJC, ESR, PtGA	0–2.59	2.60–3.19	3.20–5.09	5.10–9.40
DAS-28-CRP	TJC, SJC, CRP, PtGA	0–2.59	2.60–3.19	3.20–5.09	5.10–9.40
SDAI	TJC, SJC, PtGA, PrGA, CRP	0–3.30	3.31–11.00	11.01–26.00	26.01–86.00
CDAI	TJC, SJC, PtGA, PGA	0–2.80	2.81–10.00	10.01–22.00	22.01–76.00
PAS	HAQ, pain VAS, PGA VAS	0–0.25	0.26–3.70	3.71–7.99	8.00–10.00
PASII	HAQ-II, pain VAS, PtGA VAS	0–0.25	0.26–3.70	3.71–7.99	8.00–10.00
RAPID 3	MDHAQ-II, pain VAS, PtGA VAS	0–1.00	1.01–2.00	2.01–4.0	4.01–10.0

ACR: American College of Rheumatology; CDAI: Clinical Disease Activity Index; DAS-28: Disease activity score using a 28 joint count; DMARD: Disease-modifying antirheumatic drug; ESR: Erythrocyte sedimentation rate; HAQ: Health assessment questionnaire; MDHAQ: Multidimensional HAQ; PAS: Patient Activity Scale; PAS II: Patient Activity Scale II; PGA: Provider global assessment; PtGA: Patient global assessment; RA: Rheumatoid arthritis; RAPID 3: Routine Assessment of Patient Index Data 3; SDAI: Simplified Disease Activity Index; SJC: Swollen joint count; TJC: Tender joint count.
Data taken from [23,24].

therapeutic outcomes as biomarker applications expand beyond detection and risk identification to prognosis, therapy selection and disease activity monitoring, resulting in greater preservation of joint space and motility [7].

Previous studies have demonstrated that a ‘treat-to-target’ approach improved patient outcomes [8–10]. In RA, disease activity monitoring based on swelling and/or tender joint count along with global assessment has been widely used in clinical practice to target therapy. Improved clinical effectiveness may be achieved via the use of biomarkers in patients with early RA, in addition to the current assessment tools [11]. Recent studies have explored the use of a multibiomarker disease activity (MBDA) measure to assist physicians in treatment decisions between traditional disease-modifying antirheumatic drugs (DMARDs) and biologic DMARDs, specifically in patients who already failed a primary option [12–14]. Previous reviews introduced MBDA as an option for monitoring disease activity [12,15]. Unfortunately, they lacked analyses of the MBDA test versus traditional approaches regarding clinical [16,17]. The objective of this review was to describe the clinical utility of different approaches to monitoring disease activity in order to guide treatment strategies and to provide insight into the role of the MBDA test in a practical setting from clinical and cost perspectives.

Traditional disease activity measures in RA

The goal of therapy for RA is to maximize the patient’s long-term health-related quality of life by controlling symptoms, preventing structural joint damage, normalizing physical function and improving the patient’s ability to function in social and work activities [18]. Because RA cannot be tracked by a single domain, monitoring RA disease activity and gauging treatment responses have traditionally relied upon physician- and patient-reported responses to composite tools, such as the Disease Activity Score (DAS-28), the Clinical Disease Activity Index and the Simplified DAS [19,20]. Physicians also focus on symptoms and counts of tender and swollen joints using various imaging techniques to assess joint damage; they may also use the Health Assessment Questionnaire without Disability Index [21] and criteria from the American College of Rheumatology (ACR) and European League Against Rheumatism (EULAR) [22]. RA disease activity assessments and cut-offs to decide low, moderate and high RA disease activity recommended by ACR are summarized in Table 1 [23,24]. Of the assessment tools, DAS-28 augmented by a biomarker test result, either C-reactive protein (CRP) or erythrocyte sedimentation rate (ESR) has been widely acknowledged in a clinical setting. By using proper weighting factors, which is a key difference from Simplified DAS or Clinical Disease Activity Index, DAS-28 demonstrated its performance in measuring response to treatment and disease activity [25].

Traditional assessments have been psychometrically validated in a group of RA patients, meaning that such assessments help physicians consistently monitor a patient’s disease activity as long as the same assessment is performed regularly [20,26,27].

The key disadvantage of using traditional disease activity measures is reliability (i.e., predictability and reproducibility). A recent study revealed inconsistencies in DAS from traditional assessments [28]. From the same study, the agreement of assessments by the same physician on different visits was slightly lower than the agreement between physician and patient [28]. In conclusion, the scoring systems are meaningful as a supportive tool rather than clear treatment guidance [29]. More importantly, there has been ongoing concern about the use of a physician assessment

Table 2. Biomarkers in multibiomarker disease activity score calculation.

Biomarker	Biomarker category	Primary role
VCAM-1	Adhesion molecule	Cellular influx and tissue expansion
EGF	Growth factor	Cellular influx and tissue expansion
VEGF-A	Growth factor	Cellular influx and tissue expansion
IL-6	Cytokine-related protein	Local inflammation and destruction
TNF-RI	Cytokine-related protein	Local inflammation and destruction
MMP-1	Matrix metalloproteinase	Cartilage degradation and joint damage
MMP-3	Matrix metalloproteinase	Cartilage degradation and joint damage
YKL-40 (chitinase-3-like protein 1)	Skeletal-related protein	Stromal activity and regulation (fibroblasts, chondrocytes, and vascular cells)
Leptin	Hormone	Systemic inflammatory response
Resistin	Hormone	Systemic inflammatory response
SAA	Acute phase protein	Systemic inflammatory response
CRP	Acute phase protein	Systemic inflammatory response

leading to the overestimation of improvement and underestimation of the progression of disease activity, such as joint damage [29–31]. These traditional disease activity measures are based, in part, upon empirical and qualitative data. Results can be complicated by comorbidities and the patient's own perception of illness, resulting in further uncertainty around the patient- and physician-reported assessments on RA disease activity [32,33].

Single biomarker tests in monitoring RA

Biomarker-based DAS support treatment adjustments, potentially leading to better disease control [33]. 'Treat-to-target' guidelines specifically recommend regular, documented measurement of disease activity, especially for patients with moderate/high RA disease activity and for patients in remission [18].

Each biomarker can be used to achieve a distinct objective. For example, high-titer rheumatoid factor and anticitrullinated peptide antibody (ACPA) can help in the diagnosis and prognosis of RA [34–37]. Measuring 14-3-3 η demonstrated a greater sensitivity and specificity in reference to the ACPA in the diagnosis of RA [38]. These tests are not commonly used or recommended by guidelines, because they are often positive before RA symptoms develop and are not specific for RA [25,39]. The utility of nonspecific biomarkers, such as ESR and CRP, are limited to define acute phase reactants [25].

Although many individual biomarkers are associated with RA, single biomarkers are incomplete measures of RA activity, often lacking significant sensitivity and specificity [38]. For example, ESR and CRP often show normal results despite ongoing disease progression [38]. The sensitivity of the commonly used baseline measure rheumatoid factor is reported at 60–84% for established disease, falling shorter for new patients at only 57%, while specificity is low at 70–85% for both new and established patients [40]. These early measures miss 70–85% of patients who already present with radiographic images with early joint erosions and joint space loss [41]. Sensitivity and specificity of ACPA in RA diagnosis is dependent on the type of antibody, and on the level of RA progression at the time of diagnosis [42,43]. The response operation improved when a diagnostic algorithm included 14-3-3 η [40]. Whether the test results helped to monitor current RA disease activity, in addition to the role in diagnosis and prognosis, remains unclear [12].

Biomarkers can address the unmet need for more quantitative identification and classification of the RA disease state. Combining multiple biomarkers has the potential to allow quantitative care guidelines to be more systematically applied, while still allowing for personalized care for patients [44].

MBDA testing in RA

Our analytic validity study for MBDA identified 25 serum proteins as candidate markers for RA disease activity. Using a regression methodology, 12 of the candidate biomarkers were selected to generate a single summary score that reflects the disease activity in RA patients (Table 2). While none of these biomarkers tell a complete story individually, the MBDA test, in a patented algorithm, evaluates multiple pathways contributing to the inflammation in RA, generating a score from 1 to 100, with low (<30), moderate (30–44) and high (>44) categories [45].

We reviewed the MBDA studies that were identified from Medline on 5 March 2018 using search terms including ‘MBDA’, ‘multi-biomarker disease activity’, ‘multibiomarker disease activity’ and ‘multi biomarker disease activity’. Studies including ‘rheumatoid’ in their text were included in the review. Of the 30 studies identified from the search, only full text articles for original research relevant to the validity, reliability, clinical decision making, clinical outcomes and economics of the MBDA test were included in the review. 23 full-text research articles met this inclusion; seven did not. When the MBDA test’s brand name was included in the search, the number of articles found increased to 58. However, the number of original research articles meeting the inclusion criteria remained at 23. The review and summary of the MBDA test focused on its usefulness as a disease activity marker or treatment response marker, which can provide insight into the utility of a laboratory assessment tool in clinical practice.

When the validity of the MBDA test in determining RA disease activity was compared with traditional assessments, a significant correlation between the two was demonstrated [46]. However, changes in the MBDA score outperformed the tracked clinical assessment scores in monitoring response to treatment [47–49]. There were also significant correlations between MBDA score and multiple imaging assessments, including MRI, computed tomography, ultrasonography and radiography [50]. Limiting the analysis to each global assessment-based disease activity group, MBDA was able to provide a more precise distinction that predicted the response to an RA medication [51,52]. Compared to disease activity measures based on joint count, MBDA was not confounded by fibromyalgia or RA comorbidities [53,54]. BMI and age influenced the MBDA score, but the original MBDA score is still highly correlated with ($r > 0.9$) the BMI- and age-adjusted MBDA [53,55].

Although serologic markers alone cannot be used for diagnosis, the MBDA test has high clinical utility for disease activity monitoring in addition to or as an alternative to traditional clinical markers. Using radiographic progression as a reference measure, the MBDA test is superior to traditional assessments or CRP in predicting response across multiple medication regimens [56–60]. A 1-year follow-up study demonstrated that the order of performance in prediction of radiographic joint damage was ACPA > MBDA > DAS28 [61]. In patients who tapered or stopped DMARDs, follow-up MBDA scores were associated with RA relapse and had a stronger correlation than the association between the level of ACPA and RA relapse [62]. In the context of anti-TNFi use, the MBDA test could more accurately assess improvement associated with the use of DAS28-CRP [31].

By monitoring disease activity in RA management, the MBDA test has the potential to influence a clinician’s decision. After reviewing individual MBDA scores, physicians modified the treatment regiment for 38% of patients [63]. From three simulated patient scenarios, a 3% improvement in a quality score was observed after using the MBDA score [64]. The influence of the MBDA score on the clinical decision was associated with a short-term increase in direct medical cost but predicted longer-term cost-effectiveness [65]. Scenarios employed for these clinical utility and economic outcomes studies warrant further investigation performed in a real-world setting.

Policy implications of biomarkers in RA

The incorporation of biomarkers into treatment decision-making processes has several applications in oncology. Targeted therapy, guided by genetic and/or biomarker testing, is commonplace in multiple cancer types including breast and lung cancer [66–68]. Many of these tests have generated evidence of their cost-effectiveness in treatment decisions [67] and are part of the evaluation process in oncology value frameworks [68].

As biomarkers are considered as tools to help guide therapy in other disease areas, similar levels of evidence will be expected and evaluated through various value assessment frameworks. The AMCP Format for Formulary Submissions Version 4.0 incorporated the consideration of diagnostic testing into the description of the value of new pharmaceuticals and related technologies [69]. With the growing body of clinical evidence supporting the utility of composite biomarkers, in 2016, the Centers for Medicare and Medicaid Services began providing ongoing coverage for the MBDA test [70]. In addition, organizations such as United Rheumatology are adding biomarker assessments into clinical pathways for RA management [25].

A challenge that biomarkers present to payers is the lack of consistent balance in policy between medical and pharmacy benefit for both diagnostic tests and the treatments they guide [71]. Dichotomies often exist between policy decision makers for coverage decisions of pharmaceuticals and diagnostic tests. Clinical management tools, including prior authorization and step therapy management, are perceived to be more common under the pharmacy benefit; however, this is changing as payers attempt to address the rapid growth in specialty drug trends, according to a recent EMD Serono Specialty Digest Report [71]. Health plans will need to consider the closer integration of medical policy decision making and pharmacy spending as a key to optimizing care.

A significant challenge for specialty drugs policy will be the demonstration of value, challenging the biomarker industry to provide evidence of how targeted therapy can improve outcomes at an overall lower cost for RA and other diseases [71]. Such evidence, targeted to the specific value of composite biomarker testing in RA management, may justify the use of biomarker testing to facilitate more efficient use of specialty drug spending.

To aid future policy decisions on how specialty RA drugs would be managed, evidence should focus on how biomarkers can impact clinical decision making, policies and overall costs by optimizing the use of nonbiologic and biologic DMARDs. Economic and policy issues related to specialty pharmaceuticals must consider the patient's needs and balance innovative pathways and new technologies with affordability [72].

Health plans will need to take a more integrated, comprehensive approach to documenting the benefits of early accurate identification of RA patients likely to respond to biologic DMARDs and those that may be treated effectively with nonbiologic DMARDs. Hambardzumyan and colleagues suggested that patients with low-activity RA are likely to adequately respond to nonbiologic DMARDs, avoiding high-cost therapies [58]. This translates into improved clinical outcomes with the potential for cost-efficient use of therapeutic options.

Despite the promise of biomarkers in RA, challenges to coverage remain. In general, principles of drug coverage tend to be applied to coverage of diagnostic tests; however, these may not be the most appropriate principles to assess the value of diagnostic tests. Medical devices often do not undergo the randomized controlled trial process for regulatory approval, yet the Centers for Medicare & Medicaid Services hierarchy of evidence requests randomized controlled trial evidence of a drug treatment pathway with and without diagnostic testing. Smaller diagnostic companies with limited resources may be unable to address these hurdles. The US FDA has drafted guidance for the application of real-world data to regulatory decision making for medical devices for precisely these reasons [73]. However, in general, there is a lack of cost-effectiveness data justifying coverage for many diagnostics, although an example of such evidence in breast cancer is the 'Oncotype DX' test [67], where cost-effectiveness was clearly demonstrated. The most valuable evidence would be to show clinical utility, demonstrating that clinical decisions informed by a test result are different than decisions physicians would make without the test, and that the test guided decisions leading to improved health outcomes.

Findings of two recent studies provide insight into the use of biomarkers in cost-effective treatment decisions. A cost-effectiveness study showed that triple therapy is clinically noninferior to etanercept-methotrexate (MTX) in patients with RA, despite an Institute for Clinical and Economic Review value of over \$500,000 per quality-adjusted life year, or \$78,000 per patient over the next 10 covered years [74]. A supporting study using subgroup differentiation based on low versus high MBDA scores after MTX failure showed more patients with low scores (88 vs 35%) were likely to respond to triple-therapy than infliximab-MTX [58]. The subset of all patients studied showed that 29% had 'low' MBDA scores, making them ideal candidates for successful triple-therapy after MTX failure, while also confirming that the 71% with 'high' MBDA scores would benefit most from the high-cost biologic DMARD therapy. All things considered, later initiation of biologic DMARD for a subgroup defined by MBDA scores may potentially decrease the overall medical expenditure without a loss of clinical effectiveness. This hypothesis will have to be tested in further economic outcomes studies.

Targeted therapy (personalized medicine) offers tremendous potential to improve the delivery of healthcare services, with individual patients receiving the most appropriate treatment based on their biologic characteristics, and to provide optimal clinical outcomes at increased cost efficiency.

Discussion

Our knowledge of RA through clinical staging allows for a more detailed understanding of disease progression through precision medical testing. The understanding that RA is not a unidirectional linear disease, but rather a series of dynamic feedback loops, has led to the novel 'treat to outcome' imperative. However, much of disease modeling from a payer perspective is linear, tracking the group or average patient, rather than the individual patient, over a predetermined pathway. Patients failing a 3–6 month trial of a traditional nonbiologic DMARD, such as methotrexate, may be directly prescribed a biologic DMARD without the benefit of other therapeutic options [75]. Once on that biologic DMARD (typically a TNFi), if patients continue to show signs and symptoms of active disease, they are either given increasing doses or switched to a second biologic DMARD 94% of the time (typically to another TNF agent) [76]. Data and the 2015 ACR Guidelines show that many patients with low disease activity can safely move from a single nonbiologic DMARD to noninferior combination therapy of nonbiologic DMARDs (methotrexate, sulfasalazine and hydroxychloroquine), resulting in significant disease improvements at much lower cost than biologics [77,78]. In addition, patients failing a TNFi drug may have other inflammatory mediators driving

the RA disease activity, and thus will gain little or no value from such a change [79]. In these cases, switching to a non-TNFi biologic DMARD may offer the best response and clinical efficiency at a potentially lower cost [80].

Decades of experience with patients either on methotrexate or a biologic DMARD reveal that only 40–60% of RA patients achieve a satisfactory response as measured by at least a 50% improvement (by ACR criteria), while 15–30% develop adverse drug events [81]. As the presentation of RA moves from initiation of symptoms (baseline) to treatment, remission, reactivation or change in status, physicians need a better approach to objectively measure joint damage progression in order to better support and modify their clinical judgment.

Integrating a multibiomarker RA disease activity test more broadly into the commercial market based on real-world data may offer providers and payers validated and practical utility of subgroup identification and associated potential cost savings [46,56–58,61,62]. As an objective measure reflecting the level of inflammation, the MBDA test may be more reliable than the DAS-28 and other clinical measures [33]. Biomarker tests are reproducible numerical scales and are able to quantify RA disease activity and status.

Of the biomarkers used in RA management, based on this and previous reviews, 14-3-3 η and the MBDA test demonstrate utility in clinical practice [15]. However, the selection of biomarker tests must be tailored to optimize the value of the test. The MBDA test is a dynamic and progressive measure of disease activity versus other biomarkers that are static and only measure a single point in time. By focusing more on current disease activity monitoring, the MBDA test helps determine the next treatment decision. On the other hand, 14-3-3 η has a greater utility for a diagnosis of RA and a predictive progression marker. However, there has not yet been a direct comparison between the two options to show a clear indication for each biomarker test.

Conclusion

The targeted use of composite biomarkers in RA management paves the way for a transition from subjective measures of RA disease activity and treatment selection to more accountable, trackable and reproducible objective measures. Increased use of the MBDA test to better identify the initial inflammation stage at the joint space, eliminating sometimes misleading physical symptoms, and then using the MBDA test to track response to therapy may lead to more reliable clinical decisions. To help public and commercial payers make better informed decisions, additional evidence specifically quantifying the potential economic benefit of this multibiomarker test is required and underway. As the scientific community continues to create unique and novel medicines based on greater patient specificity and use of targeted biomarkers, the MBDA test may help standardize individual treatment decisions and serve as a model to guide therapy in diverse clinical domains.

Future perspective

The use of biomarkers has increased significantly in the area of oncology. In fact, recent FDA new drug approvals have been for cancers with specific biomarker and molecular determinants, not by the specific organ of origin of the cancer. As biomarkers become more prevalent in disease areas such as cardiovascular disease and RA, we may see a similar trend where patterns of biomarkers indicate treatment choice. In RA, where prevalence is high and biologic medications are expensive, we may see a faster uptake of biomarker testing to ensure the appropriate clinical use of more costly medicines.

Authors' contributions

Authors Lawless, Wright, Nussbaum, Elder, Oderda and Brixner made substantial contributions to the concept and design of the work as well as the analysis and interpretation of data and drafted sections of the work and critically revised the work for important intellectual content. Author Kim made substantial contributions to the concept and design of the work and critically revised the work for important intellectual content. All the authors gave final approval and agreed to be accountable for all aspects of the work.

Acknowledgements

The authors wish to thank Kelley JP Lindberg for her assistance in editing this manuscript.

Financial & competing interests disclosure

Crescendo Biosciences provided financial support for this work, and all of the authors disclose having received payment for consulting or advisory roles for Crescendo Biosciences, but publication of this manuscript was not contingent upon Crescendo Biosciences'

Executive summary

Background

- Rheumatoid arthritis (RA) is a chronic, progressive autoimmune disease affecting approximately 0.6% of US adults (1.5 million people).
- Estimated annual direct and indirect costs (i.e., loss of productivity and absenteeism) due to RA and other rheumatic conditions in the USA is \$128 billion.
- Biomarker tests may improve disease monitoring and assist clinicians in determining future treatment plans for patients who previously failed a primary treatment option, but payers need evidence of biomarker performance before using biomarkers to guide coverage decisions.
- A composite biomarker test used in RA care may be an 'optimal practice' example for policy development discussions.

Traditional disease activity measures in RA

- Traditional methods to monitor RA disease activity and gauge treatment response rely upon clinical criteria and physician judgment.
- Global assessments are complicated by comorbidities and confounded by patients' perception of the symptoms and disease progression.

Single biomarker tests in monitoring RA

- Biomarkers reliably identify and classify the RA disease state and improve disease activity monitoring. However, a single biomarker may not address all relevant domains in RA.

Multibiomarker disease activity testing in RA

- A multibiomarker approach could be a promising alternative to single marker tests and/or traditional assessments.
- By monitoring disease activity and response to therapy in a less subjective manner across multiple biologic domains, multibiomarker testing may help optimize the use of nonbiologic and biologic drugs for RA patients.

Policy implications of biomarkers in RA

- Cost-effectiveness evidence showing how biomarker-influenced targeted therapy may help physicians and health plans make more informed decisions in RA management.
- Future evidence should focus on how biomarkers can impact clinical decision making, policies and overall costs by optimizing the use of nonbiologic and biologic disease-modifying antirheumatic drugs.

Discussion

- Because biologic drugs for RA are significantly more expensive than nonbiologic drugs, objective tools that help guide treatment and optimize the use of biologic and nonbiologic drugs may improve outcomes and patient quality of life while reducing costs.
- Research quantifying the potential economic benefit of RA multibiomarker testing is needed.

Conclusion

- Composite biomarkers present an opportunity to monitor RA disease activity and guide healthcare providers to make more informed decisions between biologic and nonbiologic drugs for RA patients, improving patient outcomes and affordability.

approval. The authors have no other relevant affiliations or financial involvement with any organization or entity with a financial interest in or financial conflict with the subject matter or materials discussed in the manuscript apart from those disclosed.

Writing assistance was utilized in the production of this manuscript. KL was paid for her editing assistance by MOG, whose principals received funding from the sponsor for the production of the manuscript. However, publication was not contingent upon sponsors' approval.

Open access

This work is licensed under the Attribution-NonCommercial-NoDerivatives 4.0 Unported License. To view a copy of this license, visit <http://creativecommons.org/licenses/by-nc-nd/4.0/>

References

Papers of special note have been highlighted as: • of interest; •• of considerable interest

1. Myasoedova E, Crowson CS, Kremers HM, Therneau TM, Gabriel SE. Is the incidence of rheumatoid arthritis rising?: results from Olmsted County, Minnesota, 1955–2007. *Arthritis Rheum.* 62(6), 1576–1582 (2010).
2. Brooks PM. The burden of musculoskeletal disease – a global perspective. *Clin. Rheumatol.* 25(6), 778–781 (2006).
3. Arthritis facts. Arthritis Foundation website. www.arthritis.org/about-arthritis/understanding-arthritis/arthritis-statistics-facts.php

4. Willey VJ, Kopenski F, Lawless GD. Beyond the myths: finding benefit design solutions that address the true costs of high healthcare use. *Am. J. Manag. Care* 14(8 Suppl.), S252–S263 (2008).
- **Rather than using administrative approaches to try to reduce direct and indirect costs in chronic and severe diseases, payers will be more successful if they have evidence to help them achieve long-term cost-containment by considering targeted disease management, individual case management, health risk assessment, and early disease identification and intervention.**
5. Centers for Disease Control and Prevention (CDC). National and state medical expenditures and lost earnings attributable to arthritis and other rheumatic conditions – United States, 2003. *MMWR Morb. Mortal. Wkly Rep.* 56(1), 4–7 (2007).
6. Strimbu K, Tavel JA. What are biomarkers? *Curr. Opin. HIV AIDS* 5(6), 463–466 (2010).
7. Lindstrom TM, Robinson WH. Biomarkers for rheumatoid arthritis: making it personal. *Scand. J. Clin. Lab. Invest. Suppl.* 242, 79–84 (2010).
- **Current diagnostic methods do not adequately identify early-stage rheumatoid arthritis (RA) or identify patients' likely response to different therapies. Biomarkers have the potential to transform RA management by improving diagnosis, disease state assessment, prediction of disease progression, selection of therapy and monitoring response to therapy.**
8. Allaart CF, Breedveld FC, Dijkmans BA. Treatment of recent-onset rheumatoid arthritis: lessons from the BeSt study. *J. Rheumatol. Suppl.* 80, 25–33 (2007).
9. Grigor C, Capell H, Stirling A *et al.* Effect of a treatment strategy of tight control for rheumatoid arthritis (the TICORA study): a single-blind randomised controlled trial. *Lancet* 364(9430), 263–269 (2004).
10. Verstappen SM, Jacobs JW, Van Der Veen MJ *et al.* Intensive treatment with methotrexate in early rheumatoid arthritis: aiming for remission. Computer Assisted Management in Early Rheumatoid Arthritis (CAMERA, an open-label strategy trial). *Ann. Rheum. Dis.* 66(11), 1443–1449 (2007).
11. Gonzalez-Alvaro I, Ortiz AM, Seoane IV, Garcia-Vicuna R, Martinez C, Gomariz RP. Biomarkers predicting a need for intensive treatment in patients with early arthritis. *Curr. Pharm. Des.* 21(2), 170–181 (2015).
12. Gavrilu BI, Ciofu C, Stoica V. Biomarkers in rheumatoid arthritis, what is new? *J. Med. Life* 9(2), 144–148 (2016).
13. Yazici Y, Swearingen CJ. MBDA: what is it good for? *Ann. Rheum. Dis.* 73(11), e72 (2014).
14. Van Vollenhoven R, Hambardzumyan K, Chernoff D, Bolce R. Response to: 'MBDA: what is it good for?' by Yazici *et al.* *Ann. Rheum. Dis.* 73(11), e73 (2014).
15. Worley S. Will biomarkers be next leap forward in RA? *Manag. Care* 22(8), 46–47, 55 (2013).
16. Bossuyt PM, Reitsma JB, Linnet K, Moons KG. Beyond diagnostic accuracy: the clinical utility of diagnostic tests. *Clin. Chem.* 58(12), 1636–1643 (2012).
17. Lesko LJ, Zineh I, Huang SM. What is clinical utility and why should we care? *Clin. Pharmacol. Ther.* 88(6), 729–733 (2010).
18. Smolen JS, Breedveld FC, Burmester GR *et al.* Treating rheumatoid arthritis to target: 2014 update of the recommendations of an international task force. *Ann. Rheum. Dis.* 75(1), 3–15 (2016).
19. Smolen JS, Breedveld FC, Schiff MH *et al.* A simplified disease activity index for rheumatoid arthritis for use in clinical practice. *Rheumatology (Oxford)* 42(2), 244–257 (2003).
20. Prevoo ML, Van 't Hof MA, Kuper HH, Van Leeuwen MA, Van De Putte LB, Van Riel PL. Modified disease activity scores that include twenty-eight-joint counts. Development and validation in a prospective longitudinal study of patients with rheumatoid arthritis. *Arthritis Rheum.* 38(1), 44–48 (1995).
21. Bruce B, Fries JF. The Stanford Health Assessment Questionnaire: dimensions and practical applications. *Health Qual. Life Outcomes* 1, 20 (2003).
- **The Health Assessment Questionnaire has increased the credibility and use of validated self-report measurement techniques and has raised appreciation of outcome assessment. This article describes the Health Assessment Questionnaire's development, content, dissemination and uses.**
22. Felson DT, Smolen JS, Wells G *et al.* American College of Rheumatology/European League against Rheumatism provisional definition of remission in rheumatoid arthritis for clinical trials. *Ann. Rheum. Dis.* 70(3), 404–413 (2011).
23. Singh JA, Furst DE, Bharat A *et al.* 2012 update of the 2008 American College of Rheumatology recommendations for the use of disease-modifying antirheumatic drugs and biologic agents in the treatment of rheumatoid arthritis. *Arthritis Care Res. (Hoboken)* 64(5), 625–639 (2012).
24. Anderson J, Caplan L, Yazdany J *et al.* Rheumatoid arthritis disease activity measures: American College of Rheumatology recommendations for use in clinical practice. *Arthritis Care Res. (Hoboken)* 64(5), 640–647 (2012).
25. Clinical Practice Guideline: Rheumatoid Arthritis – Adult. Version 1.1.2016. United Rheumatology. September 2016. www.unitedrheumatology.org/united-rheumatology-clinical-guidelines/
26. Uhlig T, Kvien TK, Pincus T. Test-retest reliability of disease activity core set measures and indices in rheumatoid arthritis. *Ann. Rheum. Dis.* 68(6), 972–975 (2009).

27. Anderson JK, Zimmerman L, Caplan L, Michaud K. Measures of rheumatoid arthritis disease activity: Patient (PtGA) and Provider (PrGA) Global Assessment of Disease Activity, Disease Activity Score (DAS) and Disease Activity Score with 28-Joint Counts (DAS28), Simplified Disease Activity Index (SDAI), Clinical Disease Activity Index (CDAI), Patient Activity Score (PAS) and Patient Activity Score-II (PASII), Routine Assessment of Patient Index Data (RAPID), Rheumatoid Arthritis Disease Activity Index (RADAI) and Rheumatoid Arthritis Disease Activity Index-5 (RADAI-5), Chronic Arthritis Systemic Index (CASI), Patient-Based Disease Activity Score With ESR (PDAS1) and Patient-Based Disease Activity Score without ESR (PDAS2), and Mean Overall Index for Rheumatoid Arthritis (MOI-RA). *Arthritis Care Res. (Hoboken)* 63(Suppl. 11), S14–S36 (2011).
28. Heegaard C, Dreyer L, Egsmose C, Madsen OR. Test-retest reliability of the disease activity score 28 CRP (DAS28-CRP), the simplified disease activity index (SDAI) and the clinical disease activity index (CDAI) in rheumatoid arthritis when based on patient self-assessment of tender and swollen joints. *Clin. Rheumatol.* 32(10), 1493–1500 (2013).
29. Jensen Hansen IM, Asmussen Andreasen R, Van Bui Hansen MN, Emamifar A. The reliability of disease activity score in 28 joints-c-reactive protein might be overestimated in a subgroup of rheumatoid arthritis patients, when the score is solely based on subjective parameters: a cross-sectional, exploratory study. *J. Clin. Rheumatol.* 23(2), 102–106 (2017).
30. Matsui T, Kuga Y, Kaneko A *et al.* Disease Activity Score 28 (DAS28) using C-reactive protein underestimates disease activity and overestimates EULAR response criteria compared with DAS28 using erythrocyte sedimentation rate in a large observational cohort of rheumatoid arthritis patients in Japan. *Ann. Rheum. Dis.* 66(9), 1221–1226 (2007).
31. Reiss WG, Devenport JN, Low JM, Wu G, Sasso EH. Interpreting the multi-biomarker disease activity score in the context of tocilizumab treatment for patients with rheumatoid arthritis. *Rheumatol. Int.* 36(2), 295–300 (2016).
32. Michaud K, Wallenstein G, Wolfe F. Treatment and nontreatment predictors of health assessment questionnaire disability progression in rheumatoid arthritis: a longitudinal study of 18,485 patients. *Arthritis Care Res. (Hoboken)* 63(3), 366–372 (2011).
33. Hirata S, Defranoux N, Hanami K, Yamaoka K, Tanaka Y. A multi-biomarker disease activity score for monitoring rheumatoid arthritis. *Current Biomarker Findings* 5, 69–78 (2015).
- **Reviews the literature to describe the multibiomarker disease activity score (DAS), its development and validation, and its applications as an objective and convenient disease assessment tool in patients with RA.**
34. Shmerling RH, Delbanco TL. The rheumatoid factor: an analysis of clinical utility. *Am. J. Med.* 91(5), 528–534 (1991).
35. Luime JJ, Colin EM, Hazes JM, Lubberts E. Does anti-mutated citrullinated vimentin have additional value as a serological marker in the diagnostic and prognostic investigation of patients with rheumatoid arthritis? A systematic review. *Ann. Rheum. Dis.* 69(2), 337–344 (2010).
36. Nielsen SF, Bojesen SE, Schnohr P, Nordestgaard BG. Elevated rheumatoid factor and long term risk of rheumatoid arthritis: a prospective cohort study. *BMJ* 345, e5244 (2012).
37. Ronnelid J, Wick MC, Lampa J *et al.* Longitudinal analysis of citrullinated protein/peptide antibodies (anti-CP) during 5 year follow up in early rheumatoid arthritis: anti-CP status predicts worse disease activity and greater radiological progression. *Ann. Rheum. Dis.* 64(12), 1744–1749 (2005).
38. Kay J, Morgacheva O, Messing SP *et al.* Clinical disease activity and acute phase reactant levels are discordant among patients with active rheumatoid arthritis: acute phase reactant levels contribute separately to predicting outcome at one year. *Arthritis Res. Ther.* 16(1), R40 (2014).
39. Singh JA, Saag KG, Bridges L Jr. *et al.* 2015 American College of Rheumatology Guideline for the Treatment of Rheumatoid Arthritis. *Arthritis Rheumatol.* 68(1), 1–26 (2016).
40. Maksymowych WP, Naides SJ, Bykerk V *et al.* Serum 14–3–3eta is a novel marker that complements current serological measurements to enhance detection of patients with rheumatoid arthritis. *J. Rheumatol.* 41(11), 2104–2113 (2014).
41. Hoving JL, Buchbinder R, Hall S *et al.* A comparison of magnetic resonance imaging, sonography, and radiography of the hand in patients with early rheumatoid arthritis. *J. Rheumatol.* 31(4), 663–675 (2004).
42. Renger F, Bang H, Feist E *et al.* Immediate determination of ACPA and rheumatoid factor—a novel point of care test for detection of anti-MCV antibodies and rheumatoid factor using a lateral-flow immunoassay. *Arthritis Res. Ther.* 12(3), R120 (2010).
43. Suwannalai P, Trouw LA, Toes RE, Huizinga TW. Anti-citrullinated protein antibodies (ACPA) in early rheumatoid arthritis. *Mod. Rheumatol.* 22(1), 15–20 (2012).
44. Biomarkers Definitions Working G. Biomarkers and surrogate end points: preferred definitions and conceptual framework. *Clin. Pharmacol. Ther.* 69(3), 89–95 (2001).
45. Centola M, Cavet G, Shen Y *et al.* Development of a multi-biomarker disease activity test for rheumatoid arthritis. *PLoS ONE* 8(4), e60635 (2013).
46. Bakker MF, Cavet G, Jacobs JW *et al.* Performance of a multi-biomarker score measuring rheumatoid arthritis disease activity in the CAMERA tight control study. *Ann. Rheum. Dis.* 71(10), 1692–1697 (2012).
47. Hirata S, Dirven L, Shen Y *et al.* A multi-biomarker score measures rheumatoid arthritis disease activity in the BeSt study. *Rheumatology (Oxford)* 52(7), 1202–1207 (2013).

48. Hirata S, Li W, Defranoux N *et al.* A multi-biomarker disease activity score tracks clinical response consistently in patients with rheumatoid arthritis treated with different anti-tumor necrosis factor therapies: A retrospective observational study. *Mod. Rheumatol.* 25(3), 344–349 (2015).
49. Hirata S, Li W, Kubo S *et al.* Association of the multi-biomarker disease activity score with joint destruction in patients with rheumatoid arthritis receiving tumor necrosis factor- α inhibitor treatment in clinical practice. *Mod. Rheumatol.* 26(6), 850–856 (2016).
50. Krabbe S, Bolce R, Brahe CH *et al.* Investigation of a multi-biomarker disease activity score in rheumatoid arthritis by comparison with magnetic resonance imaging, computed tomography, ultrasonography, and radiography parameters of inflammation and damage. *Scand. J. Rheumatol.* 46(5), 353–358 (2017).
51. Curtis JR, Van Der Helm-Van Mil AH, Knevel R *et al.* Validation of a novel multibiomarker test to assess rheumatoid arthritis disease activity. *Arthritis Care Res. (Hoboken)* 64(12), 1794–1803 (2012).
52. Li W, Sasso EH, Van Der Helm-Van Mil AH, Huizinga TW. Relationship of multi-biomarker disease activity score and other risk factors with radiographic progression in an observational study of patients with rheumatoid arthritis. *Rheumatology (Oxford)* 55(2), 357–366 (2016).
53. Bouman CaM, Van Der Maas A, Van Herwaarden N, Sasso EH, Van Den Hoogen FHJ, Den Broeder AA. A multi-biomarker score measuring disease activity in rheumatoid arthritis patients tapering adalimumab or etanercept: predictive value for clinical and radiographic outcomes. *Rheumatology (Oxford)* 56(6), 973–980 (2017).
54. Lee YC, Hackett J, Frits M *et al.* Multibiomarker disease activity score and C-reactive protein in a cross-sectional observational study of patients with rheumatoid arthritis with and without concomitant fibromyalgia. *Rheumatology (Oxford)* 55(4), 640–648 (2016).
55. Curtis JR, Greenberg JD, Harrold LR, Kremer JM, Palmer JL. Influence of obesity, age, and comorbidities on the multi-biomarker disease activity test in rheumatoid arthritis. *Semin. Arthritis Rheum.* 47(4), 472–477 (2018).
56. Hambardzumyan K, Bolce R, Saevarsdottir S *et al.* Pretreatment multi-biomarker disease activity score and radiographic progression in early RA: results from the SWEFOT trial. *Ann. Rheum. Dis.* 74(6), 1102–1109 (2015).
57. Hambardzumyan K, Bolce RJ, Saevarsdottir S *et al.* Association of a multibiomarker disease activity score at multiple time-points with radiographic progression in rheumatoid arthritis: results from the SWEFOT trial. *RMD Open* 2(1), e000197 (2016).
58. Hambardzumyan K, Saevarsdottir S, Forslund K *et al.* A Multi-biomarker disease activity score and the choice of second-line therapy in early rheumatoid arthritis after methotrexate failure. *Arthritis Rheumatol. (Hoboken NJ)* 69(5), 953–963 (2017).
- **Shows that the multibiomarker DAS is differentially associated with response to subsequent treatments in RA patients who had inadequately responded to methotrexate. Thus, the multibiomarker DAS may help guide subsequent treatment to select the most beneficial treatment paths for patients.**
59. Van Der Helm-Van Mil AH, Knevel R, Cavet G, Huizinga TW, Haney DJ. An evaluation of molecular and clinical remission in rheumatoid arthritis by assessing radiographic progression. *Rheumatology (Oxford)* 52(5), 839–846 (2013).
60. Van Vollenhoven RF, Bolce R, Hambardzumyan K *et al.* Brief report: enhancement of patient recruitment in rheumatoid arthritis clinical trials using a multi-biomarker disease activity score as an inclusion criterion. *Arthritis Rheumatol. (Hoboken, NJ)* 67(11), 2855–2860 (2015).
61. Markuse IM, Dirven L, Van Den Broek M *et al.* A multibiomarker disease activity score for rheumatoid arthritis predicts radiographic joint damage in the BeSt study. *J. Rheumatol.* 41(11), 2114–2119 (2014).
62. Rech J, Hueber AJ, Finzel S *et al.* Prediction of disease relapses by multibiomarker disease activity and autoantibody status in patients with rheumatoid arthritis on tapering DMARD treatment. *Ann. Rheum. Dis.* 75(9), 1637–1644 (2016).
63. Li W, Sasso EH, Emerling D, Cavet G, Ford K. Impact of a multi-biomarker disease activity test on rheumatoid arthritis treatment decisions and therapy use. *Curr. Med. Res. Opin.* 29(1), 85–92 (2013).
64. Peabody JW, Strand V, Shimkhada R, Lee R, Chernoff D. Impact of rheumatoid arthritis disease activity test on clinical practice. *PLoS ONE* 8(5), e63215 (2013).
65. Michaud K, Strand V, Shadick NA *et al.* Outcomes and costs of incorporating a multibiomarker disease activity test in the management of patients with rheumatoid arthritis. *Rheumatology (Oxford)* 54(9), 1640–1649 (2015).
66. Adamson RT. Biomarkers and molecular profiling in non-small cell lung cancer: an expanding role and its managed care implications. *Am. J. Manag. Care* 19(19 Suppl.), s398–s404 (2013).
67. Smyth L, Watson G, Walsh EM *et al.* Economic impact of 21-gene recurrence score testing on early-stage breast cancer in Ireland. *Breast Cancer Res. Treat.* 153(3), 573–582 (2015).
68. Wilson L, Lin T, Wang L *et al.* Evaluation of the ASCO value framework for anticancer drugs at an academic medical center. *J. Manag. Care Spec. Pharm.* 23(2), 163–169 (2017).
69. The AMCP Format for Formulary Submissions. Version 4.0. Academy of Managed Care Pharmacy. (2016). www.amcp.org/FormatV4/
70. Centers for Medicare & Medicaid Services. Clinical Laboratory Fee Schedule. www.cms.gov/Medicare/Medicare-Fee-for-Service-Payment/ClinicalLabFeeSched/index.html
71. EMD serono specialty digest: managed care strategies for specialty pharmaceuticals. EMD Serono. (2016). www.specialtydigest.emdserono.com/digest.aspx

72. Hirsch BR, Balu S, Schulman KA. The impact of specialty pharmaceuticals as drivers of health care costs. *Health Aff. (Millwood)* 33(10), 1714–1720 (2014).
73. U.S. Food and Drug Administration (FDA). Use of real-world evidence to support regulatory decision-making for medical devices. Draft guidance for industry and Food and Drug Administration staff. July 27, 2016. www.fda.gov/downloads/medicaldevices/deviceregulationandguidance/guidancedocuments/ucm513027.pdf
74. Bansback N, Phibbs CS, Sun H *et al.* Triple therapy versus biologic therapy for active rheumatoid arthritis: a cost–effectiveness analysis. *Ann. Intern. Med.* 167(1), 8–16 (2017).
75. O'dell JR, Mikuls TR, Taylor TH *et al.* Therapies for active rheumatoid arthritis after methotrexate failure. *N. Engl. J. Med.* 369(4), 307–318 (2013).
76. Kamal KM, Madhavan SS, Hornsby JA, Miller LA, Kavookjian J, Scott V. Use of tumor necrosis factor inhibitors in rheumatoid arthritis: a national survey of practicing United States rheumatologists. *Joint Bone Spine* 73(6), 718–724 (2006).
77. Sparks JA, Krumme AA, Shrank WH *et al.* Brief report: intensification to triple therapy after treatment with nonbiologic disease-modifying antirheumatic drugs for rheumatoid arthritis in the United States from 2009 to 2014. *Arthritis Rheumatol. (Hoboken, NJ)* 68(7), 1588–1595 (2016).
78. Wailoo A, Hernandez Alava M, Scott IC, Ibrahim F, Scott DL. Cost–effectiveness of treatment strategies using combination disease-modifying anti-rheumatic drugs and glucocorticoids in early rheumatoid arthritis. *Rheumatology (Oxford)* 53(10), 1773–1777 (2014).
79. Bombardieri S, Ruiz AA, Fardellone P *et al.* Effectiveness of adalimumab for rheumatoid arthritis in patients with a history of TNF-antagonist therapy in clinical practice. *Rheumatology (Oxford)* 46(7), 1191–1199 (2007).
80. Sullivan SD, Alfonso-Cristancho R, Carlson J, Mallya U, Ringold S. Economic consequences of sequencing biologics in rheumatoid arthritis: a systematic review. *J. Med. Econ.* 16(3), 391–396 (2013).
- **Reviews the economic evidence of sequencing various biologic treatments after RA patients show incomplete response to initial anti-TNF treatment, showing that using non-TNF biologics in the sequence are likely to be more cost-effective than anti-TNF specific cycling sequences.**
81. Kooloos WM, Huizinga TW, Guchelaar HJ, Wessels JA. Pharmacogenetics in treatment of rheumatoid arthritis. *Curr. Pharm. Des.* 16(2), 164–175 (2010).