In an ideal scenario, a biomarker would both reveal the driver of disease and identify an effective treatment. In oncology, genetic biomarkers that molecularly or clinically classify patient populations for targeted therapies, e.g., BRAF [1] and HER-2 [2], have been clinically validated and are reaching this ideal. However, biomarkers are necessarily based on the pathobiology of the underlying disease and therefore for most diseases must be used to advance drug development and patient care in a more sequential fashion. Systemic autoimmune diseases, such as rheumatoid arthritis [3] (RA), are complex disorders that may be influenced by a variety of factors including immunological mechanisms, genetics and the environment. Biomarkers in use and under evaluation offer an important opportunity to advance clinical trial design and to change clinical practice. The biomarkers ultimately selected will reflect the complexity of these diseases.

One successful oncology biomarker example is the BRAF V600E mutation in metastatic melanoma, which defines tumors more likely to respond to treatment with a BRAF inhibitor (vemurafenib [Zelboraf [4]]). The BRAF protein, in the RAS-RAF pathway, is involved in normal cell growth and survival. However, mutations in the BRAF protein lead to uncontrolled cell growth and survival, and are estimated to occur in half of all melanomas. Detection of the mutation in tumor cells directs treatment to vemurafenib where the drug targets the mutant protein and has had impressive results for melanoma patients. This scenario is clearly ideal. However,
many diseases are not caused by a single mutant protein, and therefore the role of biomarkers in disease detection and treatment will likely be different.

Systemic autoimmune diseases include RA, systemic lupus erythematosus (SLE), Sjögren’s syndrome (SjS), polymyositis/dermatomyositis and systemic sclerosis (SSc). They are characterized by changes in adaptive immunity with autoantibodies reactive to a wide variety of autoantigens including DNA, cell surface molecules and intracellular matrix proteins. Biomarkers for systemic autoimmune diseases are needed for early disease detection, treatment guidance and patient stratification in clinical trials, as well as for treatment response monitoring. It is extremely unlikely that there will be a single biomarker that can address one of these roles, much less all of them. Rather, panels of biomarkers evaluated at different stages to inform disease detection and treatment decisions, coupled with robust, empirical evidence linking patterns of biomarkers to different treatment options, may be more scientifically feasible. This goal has not yet been realized but is achievable with good basic and applied research, systematic data collection, and data systems that can be used to integrate and share data.

RA is the most common systemic autoimmune disease and it affects multiple systems over its course, ranging from mild to severe. Biomarkers for RA diagnosis typically include rheumatoid factor (RF), erythrocyte sedimentation rate (ESR), C-reactive protein (CRP) and anti-cyclic citrullinated peptide (anti-CCP), according to the American College of Rheumatology. Measures of disease activity include the DAS28 (ESR, CRP), which calculates a disease activity score based on the number of tender and swollen joints using a 28 joint count, a patient global activity score, and ESR or CRP levels. Newer RA disease activity tests include the Vectra DA test [5], which is a panel of 12 proteins whose levels are combined into a single score between one and 100 based on an algorithm. This score is reported along with a classification of the disease into low, moderate and high disease activity.

For other systemic autoimmune diseases a variety of biomarkers are used for diagnosis and response to treatment. The antinuclear antibody (ANA) test is used to screen for the presence of autoantibodies that are directed to components in the nucleus of the cell. The ANA can aid in an autoimmune diagnosis, however it lacks specificity. For example, almost all patients with SLE have a positive ANA test, but most people with a positive ANA test do not have SLE. Other markers include the anti-dsDNA test, which can be useful in confirming a lupus diagnosis, according to the Mayo Clinic. Anti-dsDNA levels are associated with more active disease and are a risk factor for lupus nephritis, a kidney inflammation that can occur with lupus. Other autoantibody tests used for SLE [6], as well as to help diagnose other autoimmune diseases, include antiphospholipid antibodies, anti-Sm, anti-Ro (SSA) and anti-La (SSB). Anti-Ro is found in ~25 to 60 percent of lupus patients and in 70 percent of people with SjS.

Biomarker research continues for both diagnosis and progression monitoring for systemic autoimmune diseases, but faces many challenges. In contrast to single-driver mutation biomarkers that have had significant impact in oncology, biomarkers for systemic autoimmune diseases must reflect changes in biological processes. These types of mainly non-genetic biomarkers [7] can vary naturally with
age, gender and other patient characteristics. They also may vary within an individual patient based on disease flare-ups, circadian rhythms, infections and use of medications. Therefore, biomarker research must account for these variables and use proper controls and appropriate sample sizes.

The need for effective biomarkers in systemic autoimmune disease [8] is critical as many patients are only diagnosed once irreversible damage has begun, and the time for optimal treatment may have passed. Although there is seemingly a long road ahead before we can begin to match the precision of the best oncology biomarkers, advanced technology in use today can facilitate their development. Ideally, appropriate biomarker panels will be identified that can divide patients into homogenous subclasses of systemic autoimmune diseases that are paired with evidence-based treatment recommendations. Although the expected challenges are many, researchers must not become discouraged, but work together to advance our knowledge and establish biomarkers that can significantly contribute to patient care for systemic autoimmune diseases.
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