MBDA: A Valuable Tool for Medical Decision Making

To the Editor:

I read with interest the editorial by Dr. Roy Fleischmann on the limitations of the multibiomarker disease activity test (MBDA) in the management of rheumatoid arthritis (RA)[1]. He provides a comprehensive review of some of the key studies of MBDA in clinical trials and concludes that the "MBDA has not met the test of being a biomarker that can predict who will or will not respond to a specific therapy, who will or will not be able to taper or stop therapy or who will or will not have radiographic progression." While overall I tend to agree with him that this biomarker, along with ALL biomarkers, will fail to answer these questions in a binary fashion, I still disagree with his conclusions.

Medicine in general and rheumatology in particular are professions immersed in diagnostic and therapeutic uncertainty. Rheumatologists share a ritual when confronting new patients with RA of appraising their disease activity and severity, so that we can craft our treatments. This mix includes physical examinations for tender and swollen joints, measurement of acute-phase reactants and for the presence or absence of anticitrullinated protein antibodies (ACPA), doing a radiographic assessment, determining patients' reported global assessments of well-being and pain, appraising our patents' mood, assessing comorbidities (i.e., fibromyalgia) and sleep quality, and determining the patients' current psychosocial situations. We may use formal metrics (i.e., Routine Assessment of Patient Index Data 3, Clinical Disease Activity Index) or our appraisals may (too often, I fear) be completely informal. Regardless, we are constantly driven to make strong conclusions on whether to hold the course, or to taper or escalate our therapies based on varying levels of diagnostic and therapeutic certainties. For patients at the extremes there is little utility for additional tests; this reflects Bayesian reasoning that almost any test of known sensitivity and specificity, no matter how good, adds little in the setting of either very high or very low pretest probability of a given variable. Unfortunately, for most of us, our certainty is not clarion and our pretest probability is indeterminate, such as when confronting the patient with increasing pain and fatigue with modest tender but no swollen joints. We may question whether such patients are escaping from our therapeutic control or are reflecting other mitigating effects at play such as psychosocial stress, intercurrent mood problems, or other factors. Even when we are confident that such comorbid factors are present, it is often challenging to calculate exactly how much they are contributing to our patient's global distress at a given moment. It is in these settings that a biomarker can be revealing and reassuring to clinician and patient. As for prognosis, the MBDA is superior in effect size for predicting erosive disease when compared to C-reactive protein, ACPA, or any other disease activity marker and thus can serve to justify our concerns based on molecular data versus our gut feelings[2]. As Nobel laureate Daniel Kahneman has explained in his book *Thinking, Fast and Slow*, we humans tend to make the quick decisions based on thin slicing of data rather than methodologi-cally rigorous appraisals of all the data[3]. I assert that using a molecular biomarker such as the MBDA safeguards us from fast thinking, which is often vulnerable to error.

Finally, I often use MBDA initially as one tool to assess prognosis and therapeutic decision making and will frequently order it when considering initiating or changing therapy. I then generally will repeat it when the patient has arrived at a "clinical" target that is mutually agreeable to each of us, to ensure my therapy has lowered this molecular marker of disease activity and is in alignment with my clinical sense from my appraisal of traditional metrics. It is often concordant with my clinical appraisal; when it is not, I will critically reappraise our course. If the patient is in longterm remission or low disease activity, I may never again repeat the MBDA. Unfortunately, I have been doing this long enough to know that sooner or later this patient will either feel bad and look good or, less commonly, feel good and look bad, raising questions as to the character of the discordance and the relative contribution from inflammatory pathways. It is at these times that my thera-peutic decision making will be enhanced by using a molecular marker of disease activity such as the MBDA. Rheumatologists must learn to deal with uncertainty by not thinking we know all the answers or hoping a test will tell us what to do, but by recognizing diagnostic and therapeutic uncer-tainties in complex clinical settings and using objective tools to decrease them.

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