In the Search for New Treatments, Biomarkers Play Multiple Important Roles

Among the most pressing needs in the search for therapies for ALS and related disorders, biomarkers stand out for two reasons: they promise to make clinical trials faster and more informative, and while we still don't have the biomarkers we need, we are likely to very soon. Biomarker discovery and validation are among the major goals of the CReATe consortium.

A biomarker is a substance or measurement that tells us something about the disease. For instance, the level of LDL (the "bad" cholesterol) in your blood is a biomarker for your risk of heart disease.

There are several kinds of biomarkers that are relevant to ALS and the search for treatments. Right now, in most cases ALS is a clinical diagnosis, meaning it depends on the clinical exam and your report of symptoms, and your physician often needs to follow you for several months before being completely confident about the diagnosis. If clinicians had a **diagnostic biomarker** for ALS, it could allow the diagnosis to be made with certainty earlier in the disease process (assuming of course that patients with early symptoms of disease are seen by a medical professional who considers the possibility of ALS as the diagnosis and orders the test). That could allow patients to be enrolled in clinical trials very early in their disease course, which researchers believe offers the best hope of slowing the disease.

The goal of all research for ALS and related disorders is to develop new treatments, and to test them in clinical trials. Currently, trials mainly use the ALS Functional Rating Scale to determine a drug's ability to slow the disease. But a person's performance on the scale will fluctuate day to day, meaning trials must continue for many months to even out these fluctuations. A robust **progression biomarker**, something that would track the underlying course of the disease independent of daily fluctuation, could allow trials to be much shorter. This would accelerate the testing of new therapies.

Researchers increasingly appreciate that ALS is not just one disease. Instead, there are specific subtypes of ALS that affect important aspects of the disease, including progression. **Predictive biomarkers** would allow researchers to test a new treatment in a smaller, more uniform group of patients, which would also allow trials to be shorter. Predictive biomarkers might also identify subsets of patients more likely to respond to a particular therapy.

For a drug to have an effect, it must enter the central nervous system, reach the specific cells (such as motor neurons) it is intended for, and bind to a specific type of molecule (its "target") in those cells. Only then can it change the biology of the cell to alter the progression of the disease. Currently, there are very few ways to determine if a drug has entered the central nervous system, reached the intended cells, or engaged its target. **Markers for that engagement** are crucial especially when a drug fails in a clinical trial. Without such a marker, it isn't always clear whether the drug reached its target, and thus had a chance to affect the disease. With a marker, researchers can make progress faster in understanding the best kinds of drugs to use, and the best kinds of targets to aim for.

Researchers have already made progress in identifying several promising candidates for each type of biomarker, and with the field focused on their discovery, more are likely to be found and validated soon. (See also the accompanying article *The Hard and Necessary Work of Biomarker Discovery and Validation* on the 'For Clinical Researchers' page of the CReATe website.) You can contribute to the search for biomarkers of all kinds by enrolling in clinical studies. Some studies are being done to discover new biomarkers, others are testing the utility of promising biomarker candidates. Every one of these studies relies on patients. You can learn more about getting involved in these important studies HERE. [link]
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