Detecting the first hints of ALS long before clinical diagnosis may be the key to effectively slowing the disease. But for that, biomarkers for presymptomatic disease will be necessary. Finding such biomarkers is the goal of Michael Benatar, M.D., Ph.D., Associate Professor of Neurology at the University of Miami, who spoke in a recent ALS Association webinar.

“A lot damage to the nervous system has been done by the time the disease is diagnosed,” Dr. Benatar said, and one the enduring concerns of researchers is that attempting to slow the disease by beginning treatment clinical diagnosis may be giving the disease too much of the upper hand, akin to waiting until an infection is full blown before beginning an antibiotic. “We think that studying this presymptomatic period is really essential to determine whether there are opportunities to intervene much earlier in clinical trials. This is a common theme across neurodegenerative diseases, and biomarkers are essential to studying this phase of the disease.”

A biomarker is “something measurable that tells us about the risk, presence, or severity of disease,” he said, such as cholesterol for heart disease risk. The most likely place to find such a presymptomatic biomarker is in a person with a known ALS gene mutation, who has not yet developed the disease.

“A familial ALS” refers to ALS that affects more than one family member, which suggests the inheritance of a mutant gene. Presymptomatic studies in familial ALS typically involve genetic testing of unaffected members of the family. “The decision to get tested is a highly personal one,” Dr. Benatar stressed, and requires discussions with a genetic counselor.

A positive genetic test for one of the known disease-causing genes is a biomarker for ALS, since it predicts development of the disease. However, Dr. Benatar noted, not everyone with a positive test for the C9orf72 gene will go on to develop ALS; the “penetrance” of the gene is less than 100%. “Other genes may influence that penetrance,” and researchers are looking for those additional risk genes.

Other biomarkers used in ALS include motor unit number estimate (MUNE), a measure of the number of motor neurons still intact; excitability of the brain’s cortex (outermost region), which may increase ahead of clinical symptoms; and MRI imaging, which in people with ALS due to the SOD1 mutation, may show changes before the onset of clinical disease.
A critical unanswered question is whether and how these and other markers change as the disease progresses. Dr. Benatar is studying that question in multiple groups of people with ALS. “It is very important to follow these longitudinally, over time. The only way to discern whether what we measure is significant is to see if it changes over time.”

He is also exploring how the disease spreads over time in the individual person with ALS. Understanding the pattern of progression may allow researchers to learn more about presymptomatic changes in a yet-unaffected body region, such as the upper limbs in a person with initial symptoms confined to the lower limbs. This could allow researchers to predict the rate and pattern of progression for the individual person with ALS.

People who are interested in presymptomatic biomarker studies can learn more, including how to get involved, at Dr. Benatar’s website, [www.als-research.org](http://www.als-research.org), or they can contact his group by email at fals@med.miami.edu. Additional information on familial ALS and the familial ALS registry is available here: [www.falsconnect.org](http://www.falsconnect.org).

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