Bob's Last Marathon
Living the Alzheimer's Journey

TRANSCRIPT

Blood-Based Biomarkers

Almost a year ago, on *Bob's Last Marathon*, I did a podcast on biomarkers and talked about how they have transformed the way we both diagnose and understand Alzheimer's disease and related dementias. We have learned so much from MRI scans, PET scans, and lab tests of spinal fluid samples about whether and how much Alzheimer's disease is affecting the brain. With these biomarkers we can quantify Alzheimer's amyloid and tau lesions or vascular pathologies and mini-strokes that might be accumulating in the brain, causing memory loss and other cognitive problems.

We are now moving into a new era of treatment and prevention of Alzheimer's disease with anti-amyloid therapies, and biomarker tests are essential for the accurate diagnosis and staging of the disease and for monitoring response to treatment. But PET and MRI scans are cumbersome and expensive, spinal taps are considered an invasive procedure, and all require specialized facilities and personnel. This severely limits how accessible they are to most people. If only there were a simple blood test that provided the same information.

Easier, less expensive, and more accessible blood-based biomarkers for Alzheimer's have been a major goal for the medical research community over the last decade, and with new laboratory technologies, it seems we are just about there. There has been a spate of studies released in the last year showing that measuring amyloid and especially tau levels in routinely collected blood samples can be almost as accurate for diagnosing Alzheimer's disease as PET scans or spinal fluid testing.

This has been no small feat. For laboratories to measure minuscule amounts, even single molecules, of Alzheimer's tau and amyloid proteins that seep out of the brain and spinal fluid and then are dissolved in the comparatively vast ocean of blood circulating in our body, new technologies are needed. These technologies include, for example, new ultrasensitive reagents, microfluidics, and digital molecular detection. But how good are these blood tests?

If a health care provider is going to use a lab test to help diagnose a serious disease, they need to be very confident about the accuracy of the test. And so validating these supersensitive assays—comparing how well they do against gold-standard PET or spinal fluid or even autopsy tissue—has taken a lot of effort and the participation of many patients and family volunteers in research studies. The results are generally excellent with some biomarker assays, especially ones measuring phosphorylated tau. These achieve up to 95 percent or so agreement of the blood test results with PET imaging or spinal fluid results.

How should blood tests for Alzheimer's be used, now and in the future?

We are still learning, but I anticipate that over the next year or two, we will develop confidence in their accuracy and usefulness. If we are using them as a piece of the puzzle for making a diagnosis of someone's memory loss, blood biomarker results, in combination with a neurologist's or other memory specialist's evaluation, will be very helpful, even if not perfect. In the past, before we had any molecular biomarkers for Alzheimer's, a health care provider would identify typical symptoms of memory loss, order a head CT scan or MRI scan to make sure there were no tumors, strokes, or other major lesions affecting the brain, and order some lab tests to make sure that there weren't other medical issues like hypothyroidism, infections, or vitamin deficiencies that can affect memory. With this evaluation, the doctor would be right about 70 to 80 percent of the time when compared with the gold-standard autopsy examination of brain tissue under a microscope. The 20 percent inaccuracies were largely due to vascular dementia, Lewy body diseases, frontotemporal dementias, or other mixed or uncertain neurodegenerative conditions.

This might have been good enough when there weren't any specific treatments for Alzheimer's disease, only general symptomatic treatments. But now that there are treatments that specifically attack the amyloid plaques of Alzheimer's disease, we need to be as certain

as possible a person has amyloid plaques before we expose them to powerful and expensive medicines with significant risk of side effects. PET scans and spinal fluid biomarkers are considered very accurate. It looks like the new generation of blood tests will be almost as accurate, but a bit more time and experience will be required to establish the level of confidence we need. Initially, these blood biomarkers will probably be used for screening, and then if anti-amyloid treatment is considered, diagnosis will be confirmed with amyloid PET imaging or spinal fluid testing. After a bit of time, if blood biomarkers are proven to be as accurate, they will supplant PET and spinal fluid for diagnosis.

Beyond diagnosis, blood tests will be helpful in monitoring response to treatment. Response to anti-amyloid or anti-tau treatments can vary. We will want to know if a treatment is having the desired effect of lowering Alzheimer's pathology levels in the brain. If not, treatment should be discontinued. If it is working, we can see how long it takes for levels to drop to normal and use the biomarkers to decide when to stop. Blood tests are far simpler than PET or spinal fluid tests, and we can envision blood tests playing a significant role in treatment monitoring.

In addition to the accuracy and reliability of blood tests, the context in which test results for Alzheimer's disease are interpreted is critically important. Today, some tests are already being marketed directly to consumers, despite questions of their validity. I'd recommend that tests should only be used with a dementia specialist or other health care provider experienced in their use and interpretation. There is too much room for misinterpretation.

Looking toward the future, the greatest promise of blood-based biomarkers may be in the prevention of Alzheimer's disease. We know that the amyloid and tau pathologies of Alzheimer's disease in the brain begin to accumulate years, even decades, before the first signs of memory loss become evident. *If* we are able to detect Alzheimer's before symptoms of dementia start and *if* anti-amyloid therapy truly does slow or stop progression of disease, then we may have a window of opportunity for preventing cognitive decline. These are still big ifs, but with the progress being made today, we see a future where someone in their 50s or 60s can go to their primary care provider and get some blood tests to screen for cholesterol, diabetes, cancers, heart disease, or Alzheimer's disease. And if something shows up, treatment can begin, and in doing so prevent the diseases from ever taking hold.

Beyond the new blood tests for Alzheimer's disease, there are exciting advances toward blood tests for Parkinson's and other Lewy body diseases where the key protein is alpha-synuclein, as well as ALS and some frontotemporal dementias associated with a protein called TDP-43. We also recognize that there are many other factors that affect the brain which can drive degeneration and dementia. Inflammation, oxidative stress, vascular injury, and nutrient levels are some of these factors. A major theme of the work in our lab at Massachusetts General Hospital has been to profile these other drivers of disease. Everyone is different. The health factors driving your cognitive decline may be very different from the ones driving mine. Our goal is to use biomarkers to deeply understand each person's disease so that we can achieve the goal of personalized medicine, choosing the right treatment or prevention for the right person at the right time.

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