

A biomarker is a characteristic in your body such as a protein, hormone, or brain activity pattern, that can be measured to indicate the presence of or the risk for a health condition. Biomarkers are needed for accurate diagnosis, monitoring of an ongoing illness, for choosing the right therapeutic drug and/or treatment, and to determine if the therapeutic drug is working effectively. While there are now biomarkers in other brain related illnesses like Alzheimer's disease, there are currently no biomarkers for psychiatric illnesses such as schizophrenia and bipolar disorder. Over the past decade a lot of research studies have focused on understanding the genetic variations that increase the risk of an individual developing a psychiatric condition. These genetic variations are usually small differences in the DNA - the material that contains the information on how to build our body and maintain its function. These studies have looked at tens of thousands of individual DNA sequences and identified differences that are statistically more often associated with schizophrenia, bipolar disorder and other mental health conditions. These genetic findings are giving neuroscientists clues about what aspects of the brain's development and function to investigate further. An emerging theme is the importance of synapses. What are synapses? Inside the brain are cells called neurons. At birth, a baby's brain already has many neurons - up to 100 billion - and each one can be connected to many other neurons. A connection between two neurons is called a synapse. Throughout our lifetime neurons are constantly forming synapses with other neurons. As a child learns and develops new synapses are formed and some connections that are not being used are removed. We know from research in other brain related illnesses that proteins made by synapses in the brain can travel outside the brain and be used as a marker for appropriate synapse function. The brain produces a fluid called cerebrospinal fluid or CSF. The molecules produced in the brain like the proteins from synapses are released into the CSF and can travel within the fluid. CSF surrounds both the brain and the spinal cord. The body generates new CSF every day. Proteins made in the brain, like synaptic proteins, might be useful biomarkers for schizophrenia, bipolar disorder and related mental illnesses. These proteins can travel within the fluid down into the spinal cord and can be collected with a procedure called lumbar puncture. One current scientific hypothesis on how synaptic proteins could potentially be used as biomarkers in schizophrenia has to do with pruning. During adolescence as a child develops into an adult many of the synaptic connections between neurons are refined. The synapses that were not used during childhood are removed in a process called pruning. This results in fewer synapses in the brain but the connections that remain are actually more powerful and efficient. The term pruning comes from gardening. Tree and shrub branches that are weak are pruned. This results in stronger branches that produce more fruit, flowers, and foliage. This is similar to when your phone starts getting

overloaded with too many apps and you need to remove the ones that you downloaded but never used, so the apps you do use run more efficiently. The proper function of the brain depends on a fine balance of connections - either too many or too few synapses can be harmful. So how does the brain decide which connections should be removed during the process of synaptic pruning? Biological molecules such as proteins mark the connections in the brain that should be removed. One important protein for synapse removal is complement component 4 or C4. The C4 tagged synapses will then be surrounded and removed by brain cells called microglia. Removal of too many or too few synapses can result in health conditions. Based on the adolescent onset of schizophrenia and gathered scientific data, one current hypothesis is that schizophrenia may result from an increase in the C4 protein and too many of the synaptic connections being removed, also called over pruning. Another scientific hypothesis for understanding more about both schizophrenia and bipolar disorder focuses on the idea that the brain's ability to adapt and rewire itself in response to learning new things could be affected in individuals with these disorders. The neurons in our brain constantly form new connections and modify existing ones by strengthening connections that are used and weakening or loosening connections that are not used. This is often referred to as the synapse plasticity or use it or lose it. Markers for regulation of synaptic strength and connectivity are changed in individuals with schizophrenia and bipolar disorder compared to those without. Research studies such as the PBN study collect CSF and blood to measure the proteins in the fluid. They look for the quantity of C4 and other synaptic proteins scientists think may be involved in different processes that impact brain function. Researchers can measure CSF proteins from many different individuals in a research study to look for trends or biomarkers that might be related to symptoms or a diagnosis of a brain related disease. The hope is that the results from this research study will help us discover new biomarkers that can accurately diagnose or even predict health outcome for schizophrenia, bipolar and related mental illnesses and help guide treatment.