

Biomarkers and the Future of Treatment for Depression  
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*Editor's note: Doctors have a variety of drug options for treatment of depression. But there is currently no way to determine which antidepressant will work best for a given patient, which means that many people continue to suffer while their doctors try a series of medications. As Marisa Toups and Madhukar H. Trivedi write, however, many researchers have focused their efforts on developing biomarkers for depression—tests for aspects of a patient's physiology that can predict a clinical outcome. In the future, doctors may be able to screen patients to determine which treatment options will work for them, reducing the time a patient must continue to live with the effects of depression.*

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After six months, Mr. S. is finally sitting in the waiting room of a psychiatry clinic. He was reluctant to accept the referral a week ago from his primary care physician, but the antidepressant he has taken for the last two months seems to have done no good at all. His doctor reassured him that he knew Dr. R. at the university clinic personally—they attended medical school together—and that they had just caught up with each other at a conference. Dr. R. had impressed him by talking about her efforts to use evidence-based practice at the university psychiatry clinic. Mr. S.'s wife had also gently pushed him to go, and here he is.

During a long interview in her office, Dr. R. learns Mr. S.'s psychiatric history. He had never been treated for depression before this current medication trial, but admits he first felt depressed in college, after a breakup. He thought he'd get over it, but months went by and he still felt blue, tired, and disconnected. He managed to make decent grades in his classes but quit writing for the school newspaper, something he had loved and had even hoped to pursue as a career. He became isolated from friends and began to agonize and worry over every little decision. It had been almost a year before he began to feel better. Now he's not sure why he feels so bad. Things have been a little more stressful for him over the last year—his wife had their first child and a few months later he got promoted at work, but he had thought he would enjoy the challenge. Instead, he has to force himself to get out of bed each day. Tasks are accumulating around the house and he can't seem to get started on anything. His sleep is terrible; he tosses and turns for more than an hour after going to bed, then wakes up at four thirty in the morning and lies there worrying and berating himself until the alarm goes off at seven.

After learning about his symptoms, Dr. R. also wants to know about his family history and his experience with his current medication. Mr. S. tells her that his mother and sister have also been depressed. He is good about taking his pills every day and hasn't really had any side effects. Dr. R. notes that he took the lowest dose recommended by the Food and Drug Administration for adequate treatment, and wonders if increasing the dose would make a difference. However, since Mr. S. reports no improvement at all in symptoms, she decides it would be better to try something new. She could also add a second medication to the one he's currently taking, but again, since he has no improvement at all, she decides to switch.

### **Treatment Decision Making Today**

Dr. R.'s dilemma is typical of the way psychiatry is currently practiced—she doesn't have much guidance from the medical literature as to which medication to try next. Should she try one very different from his current medication? Or one in the same pharmacological class? One with a single mechanism of action or one with several mechanisms? In the end, all she can do is discuss specific risks and side effects with Mr. S. and choose a medication she hopes will at least be well tolerated. His specific pattern of symptoms—insomnia rather than sleeping too much, for example—unfortunately doesn't help her much in making the decision. At best, she can choose a drug that has drowsiness as a side effect, hoping to make the best use of something that is otherwise undesirable. She gives him a prescription and asks him to come back in a month. By then they might be able to tell whether the new medication is working.

No matter which medication Dr. R. chooses, Mr. S. has a poor chance of successful recovery, termed “remission” by clinicians and researchers. His first treatment course had about a 35 percent chance of remission after three months, and about a 30 percent chance of substantial recovery. Unfortunately, Mr. S. was in the roughly one-third of total patients who will have minimal or no improvement.<sup>1</sup> Dr. R. knows that stopping a medication he hasn't gotten well on and trying a new one leads to a slightly lower chance of remission, with the chances dropping off steeply on trials three and four.<sup>2</sup> Physicians often combine medications for patients who don't do well after two or three trials of single agents, but recent studies have shown that combinations may not work better than single agents.<sup>3</sup> Once multiple trials of single and combination treatments with medication fail, patients are considered candidates for so-called “stimulation” therapies, such as electroconvulsive therapy (ECT). ECT has well-established effectiveness but requires anesthesia and can cause substantial cognitive side effects; thus it is used fairly selectively. Scientists are also developing new therapies that aim to provide the benefits of ECT without the side effects and use of anesthesia, among them magnetic seizure therapy and repetitive transcranial magnetic stimulation.<sup>4</sup> If none of these is effective, the ultimate, and still very experimental, possibility is deep brain stimulation, in which a live electrode is placed inside the brain to directly alter activity of mood-related brain areas.

## **Treatment Matching and Biomarkers**

No one knows why some patients recover and others have no improvement, even after they spend months trying a series of medications. In fact, little is known with absolute certainty about how antidepressants improve mood. All currently approved medications for depression act in a similar way, increasing the availability of monoamine neurotransmitters in the brain. Neurotransmitters are molecules sent between neurons to communicate, and they come in many different types. The three monoamine neurotransmitters—serotonin, dopamine, and norepinephrine—share a similar chemical structure. Monoamines affect behavior by regulating motivation, reward seeking, aggression, and activity level. Since most antidepressants work exclusively or primarily by increasing levels of serotonin,<sup>5</sup> researchers hypothesized that low serotonin might be the cause of depression—the “chemical imbalance” popularized in commercials for antidepressants. However, studies that have artificially lowered serotonin levels have failed to produce depression in healthy people. On the other hand, reducing serotonin can cause patients who have been treated successfully with medication to relapse, suggesting that this theory explains some but not all aspects of depression.<sup>6</sup> Today there are several hypotheses about mechanisms of antidepressant efficacy, and all of them involve “downstream” neurobiological changes caused by the initial drug-induced changes in monoamine levels. Many of these theories are related to the biomarkers we discuss below.

In any case, we do know that antidepressants differ subtly from one another in their chemical activity; perhaps some are simply a better fit for a particular patient’s brain chemistry. Going back to our clinical example to see how this affects practice, let’s say Dr. R. can prescribe antidepressants A, B, C, and D, and that drug D—for unknown reasons—is the “Mr. S. drug.” From this perspective, Dr. R.’s challenge is to pick drug D immediately, without wasting time on trials of A, B, or C. Even if she chooses the right drug, Mr. S. will still have to wait weeks to feel better and might not recover for as long as two to three months. Unfortunately, in the worst case, in which drug D is tried last, he will wait almost a year to reach remission. Dr. R. has no test or other clinical information that will lead her to choose drug D first.

This information gap has been the target of researchers for some time, with a significant part of the effort focusing on development of biomarkers for depression. A biomarker is a measurable physiological factor or value that can be used to predict a clinical and, for mental disorders, a complex behavioral outcome. As new neuroscience discoveries have elucidated the

neurobiology of mood disorders and their treatment,<sup>7</sup> biomarkers have come to seem possible and even inevitable. But despite all the enthusiasm, we have yet to see biomarkers used in doctors' offices. The single biggest hurdle is that many of the recent discoveries have been in animals, and translating them to humans has been very difficult. First, there are no direct models of mental illness in animals—what does it mean for a mouse to be depressed? Human intelligence and social behavior are the greatest differences between us and other animals, so research into brain function must bridge a much wider gap between studies in animals and humans to get into the clinic.<sup>8</sup> Another limitation is that while researchers can study the brain directly in animals, it's impossible to do so in people without causing neurological damage; thus we are forced to rely on indirect methods such as imaging. While the effects of a hormone may be crystal clear when produced in the brain of a mouse, levels of that hormone in the blood of a human may not be easy to interpret, limiting the use of a potential marker.

Making practical biomarker development even more complex is the heterogeneous nature of depression, which is better described as a syndrome than a disease. One way to understand this is to view the clinical syndrome of depression as a final behavioral endpoint reached by many biological pathways. A single marker is unlikely to capture enough information to identify the path (or paths) that are important in a particular patient and to enable treatment choices that will act specifically where needed. Researchers are beginning to conceptualize such depression subtypes—each based on a biological pathway—as the underlying reason why drugs are only moderately effective. At present, however, no such pathway is clearly identified, probably because depression in most patients realistically has contributions from multiple pathways, and because the pathways are unlikely to be totally independent of one another. Nonetheless, researchers have developed many potential biomarkers in animals and have begun to test a few in humans.

### **The Stress Model of Depression**

One of the strongest conceptual frameworks for risk of depression proposes that chronic or severe stress is the primary cause of depression, with some people at higher risk than others at any given stress level. The intrinsic resistance to developing depression in the face of stress, called resilience, isn't fixed; the mind and environment form a recursive system in which resilience changes over time on the basis of past resilience and stress exposure. If the balance of

the stress response tips so that the brain spends too much time or easily gets stuck in the depressed state, then we say that a person has developed the clinical syndrome of depression. This model may not fully capture all cases of depression, but using it has allowed scientists to identify many potential biomarkers. There are so many potential biomarkers, in fact, that it is impossible for us to discuss even a small number of them individually in this article. Instead we will discuss categories of markers and mention only a few specific examples.

## **Genetics**

Genetic variation accounts for at least part of why some people develop depression while others do not. It also likely explains why some medications work better than others for a given person—if a genetic mutation affects the target of a particular drug in the cell, it's not likely to work. Unlike some illnesses, such as Huntington's disease or cystic fibrosis, the genetics of depression have remained elusive. Although depression can run in families, it is impossible to predict risk exactly from family history. So far, despite several large studies with enough patients to find mutations that have even moderate effect, no genetic mutations have been consistently associated with disease risk or drug response. The genetic variation probably most often studied for depression risk is called the serotonin transporter–linked polymorphic region. This region is a repeated DNA sequence in the gene for the serotonin transporter, a neuronal protein blocked by many antidepressants. The transporter cleans up serotonin after it is released from a neuron, so blocking it increases serotonin levels. The two most common versions of the polymorphic region are called “long” and “short” and have more or fewer repeats, respectively. In 2003 researchers reported that the short version seemed to make people vulnerable to depression if they were exposed to stress in childhood.<sup>9</sup> Although many studies have replicated this association, others have not, and it remains at least somewhat controversial.

## **Epigenetics**

Part of the explanation for contradictory findings in genetics is likely due to epigenetics. Epigenetic modifications to DNA alter the expression of genes. There are two main types of epigenetic changes: DNA methylation and histone modification. DNA methylation starts at conception and is responsible for a normal process of shutting off genes as they are no longer needed during fetal development. Other normal changes occur over the life span—at puberty for

example—but some others occur as a response to environmental influences and can increase disease risk. When a woman is depressed while pregnant, for example, the pattern of DNA methylation in her fetus's genome changes.<sup>10</sup> Later events, such as neglect or abuse, can also change DNA methylation patterns and lead to decreased resilience. Histone modification, on the other hand, can change rapidly and is more reversible. Histones are small protein spools that DNA wraps around inside the cell nucleus. Histone modifications control how tightly the DNA is wound, which in turn controls how easy it is to express. Studies have found that antidepressants can change the histone modification in genes related to depression,<sup>11</sup> suggesting that histone modification may be important to treatment outcome.

### **Hormones and Other Blood-Based Markers**

The genes of interest in depression, both genetically and epigenetically, tend to be part of several specific biological systems. Some are not surprising, like growth factors and hormones that control brain plasticity and health, as well as the hypothalamic-pituitary-adrenal (HPA) axis that regulates the body's response to stress. Others are less obvious, in particular the immune system and the system of brain, gut, liver, and pancreas that regulates metabolism. Most of the biomarkers currently under intense study are factors in one of these systems, and some, such as brain-derived neurotrophic factor (BDNF), have a role in more than one system. BDNF is a growth factor produced in response to numerous activities and environmental influences, such as diet and exercise. In the brain, BDNF is very important in neurogenesis, or neuron production. Low levels of neurogenesis are strongly correlated with depression. Because BDNF passes easily between the brain and peripheral circulation, levels measured in the blood are thought to be a marker of brain health. BDNF levels decrease in the blood of depressed patients, but also in that of patients with medical illnesses, including diabetes. Depression treatment brings BDNF levels back to normal, supporting its use as a biomarker.<sup>12</sup>

Researchers have also found that many factors used by the immune system's white blood cells are abnormal in depression. Often these factors are elevated, suggesting that chronic inflammation is part of the depression syndrome.<sup>13</sup> These same elevations place people at risk for heart disease and stroke, likely explaining why depressed people have higher risk of suffering those illnesses. Inflammation appears in the brains of model animals that exhibit depression-like behavior, and it is also found in autopsied brains of people who had depression. Inside the brain,

inflammation, like the lack of BDNF, caused decreased neurogenesis and abnormalities in the growth and function of neurons.

### **Neuroimaging and Neurophysiology**

Many of these neurobiological changes, if ongoing, are significant enough to cause changes in the brain's size and function that are visible on MRI scans or detectable with an electro-encephalogram (EEG). The brains of many patients with depression show shrinkage of the hippocampus and thinning of the frontal lobes.<sup>14</sup> These areas often exhibit abnormal activity on functional MRI scans; in some studies such abnormalities reverse with antidepressant treatment. Similarly, researchers can assess brain activity using quantitative electro-encephalograms (QEEG), in which mathematical analysis of brain activity of the same brain regions shows both abnormalities in people with depression and changes during antidepressant treatment.<sup>15</sup>

### **Conceptual Model of Future Role of Biomarkers**

How might all of these biomarkers relate to the treatment of Mr. S.? Let's go back over his history from the point of view of our model. At the moment of his conception, the framework for his future risk of depression was built. Genes inherited from his mother and father affected his brain growth, development, and eventual function. Epigenetic changes also occurred starting at conception. If his mother was depressed during her pregnancy, it would have changed his DNA-methylation pattern in the genes for receptors for the stress hormone cortisol, so that he has more difficulty adapting to chronic stress. During his college episode of depression, under the action of his abnormal stress response, neurons lost connections and made new ones that reduced his future resilience. The long-term HPA-axis abnormalities also led to increased expression of some inflammatory markers and decreased expression of growth factors. This in turn led to a decrease in neurogenesis, making him even more vulnerable, so that now he has experienced an episode of depression despite not having a severe stress burden.

We can imagine, in the future, Dr. R. ordering a blood panel of inflammatory markers and growth factors. Seeing a pattern of elevations consistent with the inability of the HPA axis to respond to long-term stress, she prescribes a medication that supports neurogenesis. After obtaining a baseline QEEG analysis, she sees Mr. S. again for a one-week follow-up, at which

the test is repeated. After examining the results of the follow-up testing, she might recommend an exercise program designed to increase circulating BDNF and reduce inflammation through a different set of pathways. If the tests had shown insufficient change after the first week, she could have changed medications or prescribed a combination of drugs and then tested again. It's even possible that testing could suggest and help support insurance coverage for treatments like psychotherapy, specific diets, or exercise, so that patients could avoid medications entirely. It's still too early to know exactly which markers will be the most useful and how they will work in practice. We can be sure, however, that the challenges of translating findings from animals to humans for this complex illness will be significant. Nonetheless, psychiatry stands to be radically changed by the development of biomarkers—to the benefit of patients everywhere.

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