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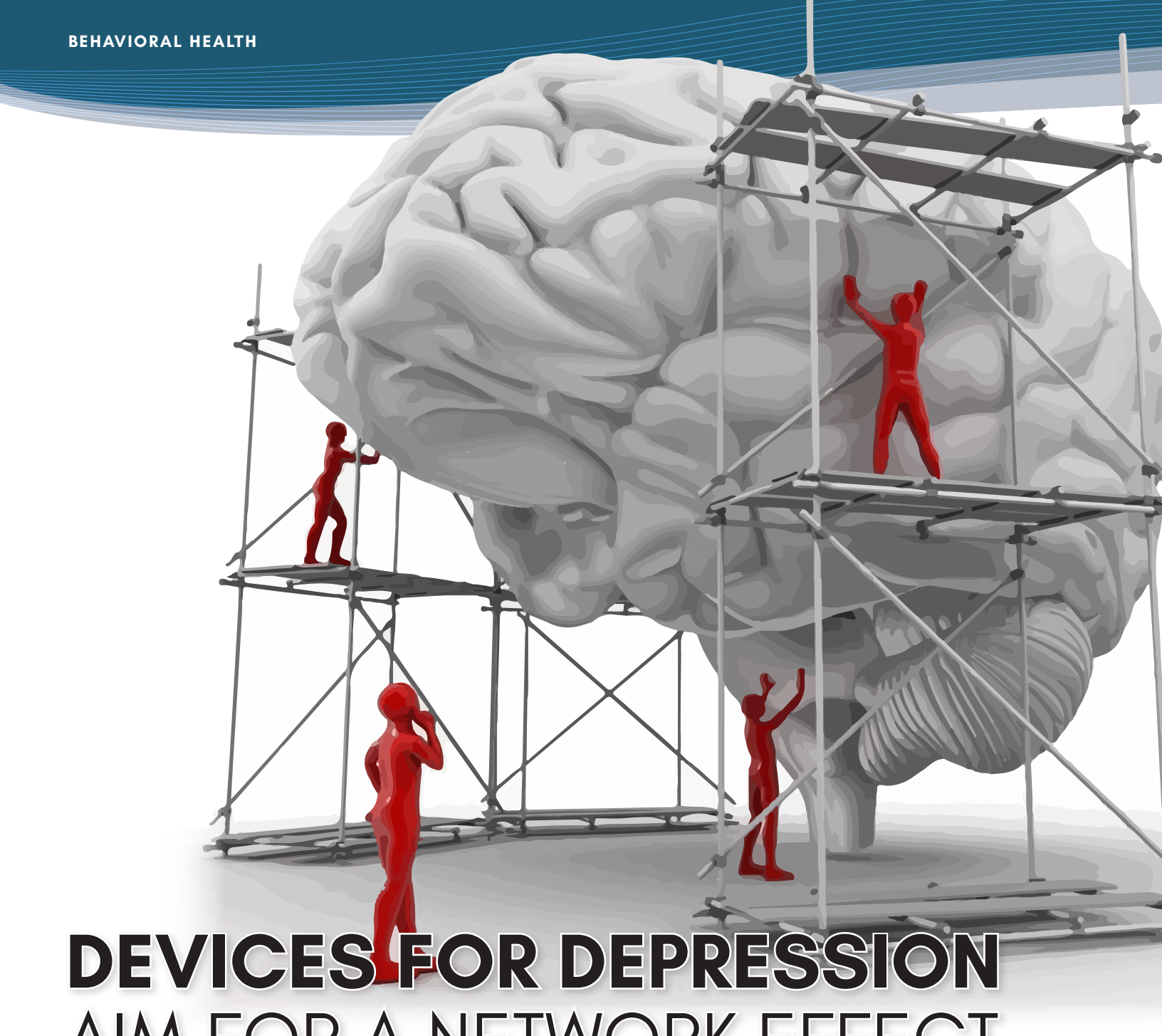


DEVICES FOR DEPRESSION AIM FOR A NETWORK EFFECT

In-clinic TMS has established itself as a safe, but only moderately effective therapy for treatment-resistant depression. To help the most critically ill depression patients, Magnus Medical looks like it has figured out how to boost both the speed and efficacy of TMS by targeting brain structures able to generate a network effect. Will it open the door to other markets in depression and mental health?

▶ MARY STUART

We can thank the pandemic, once again, for highlighting gaps in medicine and new ways to address them. According to one poll, in January 2021, four in 10 adults in the US reported symptoms of anxiety or depressive disorder, a vast increase over a survey conducted in early 2019 when one in 10 persons were depressed or anxious, a comparison that will surprise nobody. With this has come increasing recognition that depression is a comorbid condition that makes outcomes worse for just about every other disease, including COVID-19, which is itself linked to depression, either because of its impact on the immune system or simply the trauma of the disease.

At the same time, mental health has become a hot target for investment. Rock Health reported that in 2021, digital health start-ups focusing on mental healthcare (sometimes with service components) had raised $5.1 billion, $3.3 billion more than any other clinical indication that year, and almost twice the amount invested in the space in 2020 ($2.7 billion). These deals are largely focused on the delivery of care and issues of access, but this is one trend that will have an impact on therapy developers as well.

Indeed, therapeutic device company **BrainsWay Ltd.**, which has three FDA clearances for its *Deep TMS* system (for depression/anxious depression, obsessive compulsive disorder [OCD], and smoking addiction), sees tailwinds for its transcranial magnetic stimulation (TMS) business from increased access to care, the impact of COVID-19, decreasing stigma, and physician education (as noted in its March 2022 corporate presentation).

TMS and other noninvasive device therapies have a great opportunity in depression, which is not only widespread—17.3 million people in the US suffer from major depressive disorder (or, 21 million suffer from depression/anxious depression), it's also at the head of the list of the leading causes of disability, according to the World Health Organization (see *Figure 1*).

Despite the availability of 30 distinct drugs across four classes, half of all depression patients are resistant to treatments, because they become tolerant or because of the relapsing nature of their disease. One landmark study suggests that coming up with more drugs isn't necessarily the answer. The STAR*D study sponsored by the National Institute of Mental Health (Sequenced Treatment Alternatives to Relieve Depression), which studied 4,041 patients over seven years, found that patients who fail to benefit from two antidepressant treatments have a low likelihood of achieving remission with additional medications.

And depression is by no means a benign disease. Two percent of people who've ever been treated in an outpatient setting will die by suicide, and for those who have been treated in an inpatient setting, the risk doubles, according to one report.

TMS: A Safe, Noninvasive Treatment for Depression

This level of unmet need is why TMS, an atypical device therapy that requires patients to go to clinics for daily treatments for weeks on end, has found a role in depression care. **Neuronetics Inc.**, the creator of the category with its 2008 FDA clearance and still the market leader today, having treated 115,000 patients in 4 million sessions, reported revenues of $55.3 million in 2021. Second-mover BrainsWay reported 2021 revenues of $27.7 million.

Over the past 24 years, TMS has established itself as a safe, noninvasive therapy for mood disorders that avoids the side effects of drugs and comes without serious adverse events. It's reimbursed under three CPT codes by Medicare and by most major insurance companies for patients who meet eligibility requirements (they must first try without success two to four different drugs or classes of antidepressants, depending on the payor).

TMS is moderately effective in treatment-resistant depression. Neuronetics reports that in real-world settings, one-half of patients responded to its *NeuroStar* TMS therapy (often generically referred to as rTMS, for repetitive TMS), whereas one-third were in remission by the end of the treatment. Among responders and remitters, two out of three patients maintained the symptom levels they had reported at the end of the treatment phase. The clinical trial supporting the *Deep TMS* therapy of BrainsWay reported treatment response rates of 38.4%, remission rates of 32.6% and durability of the effect in 50% of responders at one year. These are modest efficacy levels, but these patients are intractable, having gone from one drug to another without experiencing durable relief from their disease.

TMS works by inducing electrical fields in the brain to depolarize cortical neurons. This is accomplished by pulsing electrical current through a coil or helmet placed on the head to produce a high-energy magnetic field that passes through the scalp, skull, and meninges to excite neuronal tissue. TMS devices, which are large and expensive, have developed as an alternative to transcranial direct electrical stimulation (tDCS), which can be made much smaller and portable, but the latter's ability

to deliver enough power to induce rapid changes in the cortex is limited by the danger of burning the scalp. (There is an emerging home-use device market around the less powerful tDCS, which is still experimental, and *MedTech Strategist* will cover companies in that space in the future.)

TMS is delivered in a clinical setting—a psychiatry practice, for example—according to the different protocols of individual manufacturers. The first two TMS systems used in the outpatient setting require one treatment session per day (that lasts from three to forty minutes, depending on the protocol) five days a week for a course of therapy that lasts four to six weeks with additional treatments following the initial course, depending upon the manufacturer and TMS system.

Newer companies offering minutes-long treatment sessions by using intermittent theta burst stimulation (iTBS) have more recently entered the market with FDA clearances for major depressive disorder, including **Nexstim PLC** (Helsinki, Finland), with a product called *NBT* (navigated brain technology) and the *CloudTMS* system of **Neurosoft TMS** (Ivanovo, Russia), both cleared in 2017. In 2018, **MAG & More GmbH** (Munich, German) gained FDA clearance for its 19-minute per treatment *Apollo TMS* therapy in May, followed in August by the *Express TMS* iTBS system from **MagVenture** (Farum, Denmark). The **Magstim Company Ltd**. (Whitland, UK) gained 510(k) clearance in October 2021 for its three-minute iTBS treatment for depression.

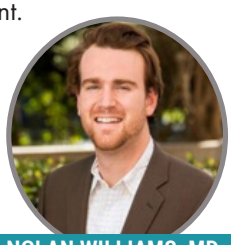
Not Just Another TMS Company

The non-invasive treatment market for depression is competitive, and somewhat confusing, because independent studies tend to refer to approaches like TMS as if it's a generic category (it's often difficult to identify the manufacturer). Some parts of TMS platforms can be protected by IP and others can't.

So, the bottom line for differentiation in the noninvasive device market for depression must be the gold standard in the medical device world: superior clinical data. This can be difficult to tease out, since very few companies have conducted large, randomized double-blinded studies. That's the next step for **Magnus Medical Inc.**, a company that offers clear differentiation, starting with, among other things, its initial focus on the inpatient treatment market for major depressive disorder. Results from a well powered investigational double-blinded randomized controlled trial evaluating a new type of non-invasive treatment protocol suggest it has the potential to be a reproducible, rapid, and highly effective treatment for severe, refractory depression in a broader clinical setting. It's still early, but the data indicates Magnus Medical will have the most differentiated platform in the space, with unprecedented efficacy in depression.

Magnus Medical: A Personalized Therapy for an Individual Disease

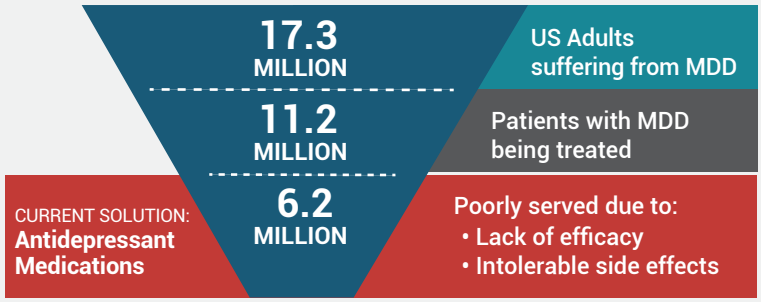
Magnus Medical, which was officially founded in December 2020, has raised a $25 million Series A round on the strength of clinical trials that suggest the company's noninvasive device therapy has profound efficacy in a particular population of patients with drug-resistant depression. Also, in October 2021, the FDA granted its Breakthrough Device designation to the Magnus neuromodulation therapy. These are impressive milestones for such a young company, but its pedigree goes a few years back to Stanford University, from which Magnus Medical licensed its novel depression treatment.


NOLAN WILLIAMS, MD

As often happens with innovation, the spark came from two clinicians, who, in caring for patients, thought there had to be a better way: Nolan Williams, MD, assistant professor within the Department of Psychiatry and Behavioral Sciences and the director

Figure 1
The Need in MDD

PATIENTS WITH MAJOR DEPRESSIVE DISORDER ARE UNDERSERVED



The medical industry has relied on pharmaceuticals as the first line treatment for MDD

3 out of 5 patients treated with medication are underserved

MDD is a leading cause of disability and a major contributor to suicide worldwide

300 million people worldwide living with depression

• 3% incidence rate

Economic burden in US of $210 billion annually

Source: Neuronetics November 2021 Investor Presentation

of the Stanford Brain Stimulation lab (at the Stanford University School of Medicine) and psychiatrist and neuroscientist Brandon Bentzley, MD, PhD, the former director of Innovation at the Stanford Brain Stimulation Lab and now chief scientific officer of Magnus Medical.

Williams describes the suffering of patients for which very little could be done—the 500,000 suicidal patients who are hospitalized with major depressive disorder each year. He notes that with other diseases of the body, it's generally the case that the more severe the disease is, the more treatment options there are—for example, in heart disease, there are thrombolytics, pacemakers, catheters and stents, and so forth. But for the most severe cases of depression, physicians don't have many solutions, at least there is nothing "scalable," as Williams puts it, since delivering psychotherapy services to patients under surveillance in the hospital for weeks on end just isn't feasible.

Patients hospitalized for major depressive disorder are often resistant to pharmaceutical therapies and other therapies like implantable vagus nerve stimulation as well. Current iterations of transcranial magnetic stimulation (TMS), at least seven versions of which, as noted, are FDA-cleared for the treatment of drug-resistant depression, won't work for the acute setting because it takes six weeks or more to achieve remission. (Depression therapies are described in terms of response, i.e., at least a 50% improvement in symptoms, and remission, the absence of symptoms.) The only option with efficacy for the depression inpatient is electroconvulsive therapy (ECT).

ECT, which passes electric current through electrodes placed on the head to induce a seizure, has improved over the years since it was first introduced in 1938. It is a rapid-acting and effective therapy for major depressive disorders that yields reported remission rates of 60%, but only 1.5% of eligible patients get it, for several reasons. First, notes Williams, 90% of hospitals don't offer ECT, and even among psychiatric hospitals, only 10% have the capability. And many people just don't want ECT because of potential side effects that include cognitive impairment, and the stigma associated with the treatment. It also takes several weeks for ECT to induce remission.

Thus, the potentially suicidal patient who comes into the emergency room often faces a long wait for a bed in the psychiatric unit—sometimes days. They'll wait in a bed in the hallway of the ER and at some point, if they haven't been admitted yet, a psychiatrist will meet them there and begin the process of tweaking the same medications that are available on an outpatient basis, which probably won't help since many of these patients will belong to the class of 5.5 million treatment-resistant depression patients. They remain in the hospital for one to three weeks then they're discharged, at which point the risk of suicide triples.

Boosting the Power of TMS

Williams, Bentzley, and their team at Stanford chose to build on the history of noninvasive TMS to see if it could be effectively condensed down to the timeframe of an inpatient psychiatric admission, as an alternative to ECT for major depressive disorder. They seem to have succeeded with SAINT (Stanford Accelerated Intelligent Neuromodulation Therapy) for treatment-resistant depression. SAINT looks like it can accomplish within five days what no TMS depression therapy can in six or more weeks, at least according to Stanford's small clinical trials to date.

In late October 2021, investigators published results of a double-blind randomized controlled trial that was stopped at the pre-specified interim analysis point because of outstanding efficacy. The 29 patients in the trial were between the ages of 22 and 80 and had, on average, suffered depression for nine years, although one elated responder had lived with depression for 45 years. Remission rates of almost 80% were seen in the active treatment group after five days of treatment (and only 13% in the sham arm of the study), and those results confirmed SAINT's earlier open-label studies that found 90% remission rates after five days.

The Stanford team had the benefit of looking at many TMS studies over the years. "A lot of good science has allowed us to do this," says Williams. "We stand on the shoulders of a lot of giants." The innovations of SAINT fall into several areas: dosing, a neurobiologically based treatment interval (described among Williams' areas of subject matter expertise as "spaced learning theory in the application of neurostimulation techniques"), and, perhaps delivering the most impact, a specific brain target and the ability to personalize that target to the patient in treatment.

"The brain is not one-size-fits-all," says Williams. "There are some commonalities and differences to everybody's brain networks." He notes that TMS systems in the past have delivered therapy, through head coils or a helmet, to a general average point in the prefrontal cortex, based on external measurements of the patients. The SAINT researchers refined that target to the spot where the left dorsolateral prefrontal cortex (dlpfc) is most closely connected to a deeper structure, the subgenual anterior cingulate cortex (sgACC). In patients with depression, the dlpfc is underactive and the sgACC is overactive. It's the job of the dlpfc to govern the sgACC, so stimulating at that point restores the healthy relationship. "We are having a network effect," says Williams.

Williams points out that based on previous TMS studies, it is evident that the further therapy delivery is from that "sweet spot," the lower the efficacy of the treatment, and that's consistent with what is already understood about deep brain stimulation. "Deep brain stimulation for Parkinson's disease is very effective, and a lot of time was spent on determining

exactly where to place the lead. Conventional rTMS is still based on an average point in the brain."

Locating the patient-specific therapy target is accomplished by imaging a patient with both structural MRI and resting state functional connectivity MRI, to find the point where the dlpfc is connected to the deeper network. During treatment, a neuronavigation system is used to ensure that the coil is placed in a position that achieves the desired targeting.

The therapy itself consists of a five-day course of high-dose intermittent theta burst stimulation delivering 1,800 pulses per session, 10 sessions a day. Between sessions, there is a 50-minute interval. This protocol respects the spaced learning theory of the brain, which finds that neuroplastic changes are more durable when a stimulus is repeated while allowing an appropriate interval of rest. As noted, most of the existing TMS therapies rely on one session of treatment per day over a much longer course of therapy.

Magnus Medical co-founder and CEO Brett Wingeier, PhD, notes that these aspects of the therapy have created a large body of IP for the company. "The core portfolio for SAINT has, among other things, issued IP on the targeting, the method for pulling out this information from fMRI and using it to create a personalized target. There is IP on the timing of the sessions, and the overall dosing, which is key to having this profound effect." He notes that there is also IP on other parts of the portfolio that are "forward-looking and related to personalization for other applications," which potentially include other degrees of depression and obsessive-compulsive disorder.

BRETT WINGEIER, PHD

In Depression, An Unprecedented Magnitude of Effect

Wingeier came in when, with IP issued and positive clinical studies published, it was time to bring this therapy to patients. With one of the SAINT group's original founders and an exclusive license to the IP from Stanford, he co-founded Magnus Medical, which is named after the profound magnitude of effect of the therapy.

Clearly, Wingeier is the right person for the job. With a PhD in biomedical engineering, he joined NeuroPace out of graduate school as principal engineer. There he worked for 13 years on the first responsive neurostimulation device for epilepsy. In 2019, he left to co-found and lead Halo Neuroscience, which developed a headset for the delivery of transcranial direct current stimulation of the brain, initially to enhance human performance in consumer markets (e.g., helping athletes improve muscle memory). "We made and sold 25,000 brain stimulators," he says, before **Flow Neuroscience** bought the platform (technology, R&D, and patents) for use in its depression therapy in February 2021. (*See "Flow Neuroscience: A Shock to Depression's System,"* MedTech Strategist, *November 27, 2017*.)

Not only did Wingeier bring commercial neuromodulation experience to Magnus, he also brought trusted investors. Andrew Firlik, MD, managing partner at Jazz Venture Partners, which invested in Halo's A and B rounds, participated in the Magnus Series A round. Heath Lukatch, PhD, invested in Halo when a partner at TPG. He is now founder and Managing Partner of Red Tree Venture Capital, which co-led the Magnus Series A round. "It's important to have this level of trust with investors because everything comes back to the data and the value that you can build in the clinic. You must respect the science and the timeframes can be long," Wingeier says.

Now Magnus Medical will push forward with larger double-blinded clinical trials to further to prove out the early promise of its technology and to build toward robust adoption and reimbursement. "This is a once-in-a-lifetime project," Wingeier says. "The effect size is profound, and there is an enormous need. We have teed up what we need to make an enormous difference."

A Treatment, Rather Than a Technology

The inpatient market for major depressive disorder is only a subset of the broader market for treatment resistant depression, but it allows the company to prove its technology for the greatest clinical need and for the individuals who are the most difficult to treat. Obviously, SAINT has advantages in speed and efficacy for the existing in-clinic market. Wingeier notes, "Magnus is a treatment company. Our core technology lies in providing personalized neuromodulation that is individually targeted to functional brain networks." Today, he says, the technology behind the treatment delivers magnetic pulses, and like any business at this stage the company must focus on its core effort, which is the SAINT treatment delivered via magnetic pulses in the clinic or hospital. "In the future, I'm confident that we can deliver personalized treatment via multiple modalities or 'physical layers.' That said, as a technologist, I'm also optimistic that TMS hardware can eventually be made much smaller and much more efficient."

From the clinician's point of view, we asked Williams if it's finally the era of mental health, after so many decades as a backwater in interventional medicine. He responded, "People do see it differently than they did 10 years ago. This is not a matter of mind over matter. People need to be aware that there is a biological component, and we can treat that." MTS

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