

HealthRhythms' Innovation, Implications for Future Research, and Potential Impact on the Human Condition.

Innovation

Many companies have tried to capitalize on the ubiquity and intimacy of the smartphone to measure aspects of mental health and to intervene in mental health conditions, but none has had the advantage of basing their measurement or intervention on a conceptual model that had been systematically validated well before the advent of digital technology. Unlike other offerings in the digital mental health space, the HealthRhythms' Cue platform draws on decades of clinical and laboratory research documented in hundreds peer-reviewed publications, many written by HealthRhythms' cofounders, on the relationship between behavioral routines or 'social rhythms.' We use that research as the basis for the design of the Cue platform and for determining which aspects of behavior are essential to mental health. This means that not only are the behaviors we focus on monitoring relevant to mental health, but they have been selected for their specific relevance to the circadian and social rhythm regulation conceptual model that has informed the questions addressed in these decades of research.

Another differentiator of our technology is the strong background of co-founders Frank and Kupfer in the science of measurement development. Dr. Kupfer had already been central to the development and validation of the Pittsburgh Sleep Quality Index (PSQI), now the world-wide standard for measurement of sleep problems in pharmaceutical company trials and academic sleep research. Using that measurement expertise, in the 1990's Drs. Frank, Kupfer and colleagues had developed a now widely used self-report instrument, the Social Rhythm Metric (SRM), to assess the daily routines or 'social rhythms' central to the social zeitgeber model; however, we recognized that long-term adherence to its daily completion requirement was an unreasonable expectation. The smartphone offered the promise of an automatic, effortless SRM that would be orders of magnitude more accurate than the patient's self-report. Indeed, our team's first pre-founding collaboration was the development of just such a mobile SRM equivalent, an effort that was rewarded by winning the Heritage Health Prize for the most

promising new technology at the 2013 Health Datapalooza conference. That recognition provided the impetus for the founding of HealthRhythms.

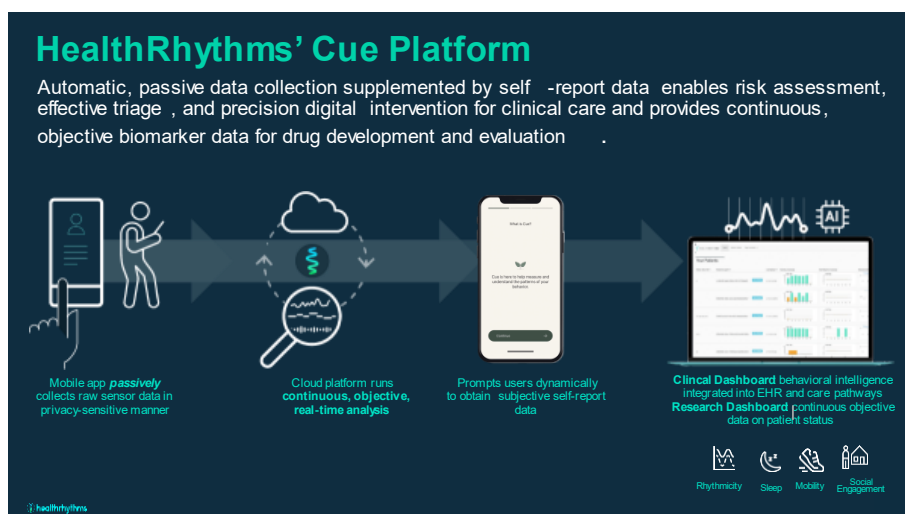
Literally, from the outset of HealthRhythms' life as a company, our Cue platform has enjoyed acceptance as providing valuable digital biomarker and treatment response data to both large pharmaceutical companies and smaller biotech companies. To date, we have been involved in providing digital biomarkers for seven pre- and post-marketing trials involving thousands of patients and hundreds of thousands of patient days of continuous, objective behavioral measurement. In each instance, the passively sensed data and inferences our platform provides were available to the site and clinical research organization (CRO) personnel for each patient the trial in real time on a 24/7 basis throughout the duration of the trial.

In addition to our unique conceptual model, HealthRhythms' co-founders' pioneering work in digital measurement sets us apart from virtually every other company in the digital phenotyping area (See document, History of the Development of the Cue Platform, for a description of Drs. Matthews and Choudhury's foundational work) . This work has formed the basis of methods for extraction of the 24/7 behavioral data streams that enable us to make more than 50 mental-health related inferences about patients' clinical status. In our initial clinical care deployment within the University of Colorado Health System (UCHealth), our platform runs as an SDK through UCH's patient experience app. Furthermore, we were able to fully integrate our platform into UCH's EHR in less than four months, enabling providers throughout the system to see the data we provide on their patients' status in real time as part of the provider's regular access to the UCHealth's electronic health record (EHR).

Our mental health-related inferences have enabled us to develop the first vital signs for psychiatric medicine. We have just completed a series of analyses demonstrating that these objective Behavioral Vital Signs have clear relevance to patients' clinical status. Briefly, we examined a series of our passive sensing features reflecting sleep, activity, and social engagement – key components of the social zeitgeber model - as they relate to self-reported depression severity in a group of 131 psychiatric outpatients followed for a period of four months. We found that individuals with more variable sleep end times across the study period reported significantly

greater depression relative to those with less variable sleep end times. In addition, our analyses indicate that on a given week, having a reduction in step count, slower walking rate, less regularity in the pattern of places visited outside the home, more time spent, and lower distances traveled from home, relative to one's own typical levels, were all associated with significantly higher depressive symptoms for that week. Such behavioral biomarkers have considerable potential value both in pharmaceutical company trials and in the context of patient care. What is perhaps most important is that each of the significant relationships we found between our inferences and patients' report of depression severity represent clinically actionable measures of patient behaviors in much the same way that the vital signs that are standard in physical medicine serve as guides to specific interventions on the part of the physician.

When we refer to the Cue platform as it is deployed in pharmaceutical clinical trials and in large integrated health systems, we are referring to both the patient-facing app that collects the individual patient's data and the clinical trial personnel- or individual provider-facing dashboard that displays the data for all the patients for whom he or she is responsible. For pharmaceutical company trials, our dashboards are configured to meet the patient tracking needs of the personnel at the individual study sites, as well as the needs of the company or CRO personnel who need to track the progress of the entire study. In the health system context, patient data are displayed in a manner permitting increasing levels of detail about the provider's panel of patients. The figure below provides a schematic of our platform, illustrating the pathway from the patient-facing app to the provider or research study personnel-facing dashboard.



The Cue platform begins with the patient's own smartphone and can run on any smartphone still available, from the least expensive Android to the most expensive iPhone. We use the GPS, accelerometer, gyroscope, and screen on-off sensors that are available on all smartphones to extract more than 50 specific inferences about patient behavior. We categorize them into four broad areas: 1) the **rhythmicity** or regularity of routines in the patient's life, 2) the extent, duration, and kinds of **physical activity** in which the patient engages; 3) validated proxies for **sleep parameters** including bedtime, wake time, sleep interruptions, regularity of the timing of sleep relative to clock time, and duration of sleep, and 4) validated proxies for **social engagement** that depend only on these passive sensors. We do not invade any of patients' private information. Our inferences do not depend on patients' social media posts, texts, emails, or voice data.

The sensor data are destructively processed on the patient's phone before they are uploaded to our cloud where we perform real-time continuous analysis of patient behavior. The results of these analyses can be used to dynamically prompt requests for self-report completion in clinical care settings. Clinical care patients receive easily understood feedback, in the form of small graphs or charts on their phone indicating how they are doing clinically. In both clinical care and research settings, the results of the continuous analysis of sensor data are immediately displayed on dashboards that can inform clinical decision-making or, in the research context, provide real-time objective assessment of patient status to study personnel.

In our digital intervention platforms, we use our behavioral inferences to determine which aspects of the patient's behavior are impeding recovery. We then send very light, single phone screen suggestions for behavior change consisting of highly personalized, just-in-time micro-interventions to move the patient in the direction of more the more regular daily routines shown to be associated with clinical recovery. We have now automated the selection of these micro-interventions from a library of more than 1500 possibilities and are evaluating the efficacy of this automated approach in an NIAAA-sponsored trial of our digital intervention platform for sleep problems in individuals in early recovery from alcohol use disorder.

The figure below provides more detail of how the provider dashboard enables clinicians to obtain a quick overview of their patient panel. Patients are color-coded by level of clinical concern based on HealthRhythms' behavioral inferences, with red indicating the patients demonstrating the greatest level of concern, amber for those with whose passive sensing data indicate moderate levels of concern, and green for those patients who appear to be doing well. The dashboard then allows the provider to click on the patient's 'attention indication' line to see graphs of the specific 24/7 passively acquired sensor data evidence supporting the attention indication.

Patient list				
Search Keywords, date, name				
^ Emergent				
Name	Date of birth	Sex	Diagnosis	Attention indication
4 Mina Miller <small>User ID: us-east-1:23cd8a7f7-a217-410d-a70d-419b4e05d226</small>	2-24-78	F	Bipolar II ADD GAD	Increased ++ sleep duration Has not left home X 8 days
^ Urgent				
Name	Date of birth	Sex	Diagnosis	Attention indication
3 Jack James <small>User ID: us-east-1:23cd8a7f7-a217-410d-a70d-419b4e05d226</small>	7-21-91	M	MDD, recurrent CVD	Decreasing activity metrics last two weeks
^ Medium				
Name	Date of birth	Sex	Diagnosis	Attention indication
2 Jessie Smith <small>User ID: us-east-1:23cd8a7f7-a217-410d-a70d-419b4e05d226</small>	9-10- 52	F	Cyclothymia	No indication of increased symptoms X 3 months

Not surprisingly, both patients and providers have had positive reactions to the experience of these new adjuncts to care. One patient participating in our initial deployment of our measurement platform within the University of Colorado Health System (UCH) said, *"I was very surprised when I got a call to check in on me because my anxiety scores had increased. I hadn't thought about it when I was answering the survey, but once I was told this, I realized that my anxiety actually had increased lately. I think this showed me that sometimes my mental health can change without me knowing it."* Another patient noted, *"... it gave me reassurance that*

"someone" was keeping an eye on me. Although I've managed to keep my anxiety attacks or episodes of psychosis to nearly zero, those tend to creep up on me and the app gave me reassurance that my behavior is better monitored and would allow me to intervene prior to the attack. it gave me reassurance that that my behavior is better monitored and would allow me to intervene prior to the attack."

UCHealth providers noted that the platform provided them with information they would not otherwise have had and information that was directly actionable: *"...the sleep section was the most useful for me to review. I am very surprised that one of my pts is only averaging about 5 hrs/sleep per night so that is definitely something we will talk about."* Another commented that *"The more frequent assessment was great. I don't think patients remember their condition more than a few days. It was great for knowing when people were OK. It works for surveillance. Then when things change, you can be right on top of it. I was able to reach out to a couple of patients based on worsening in the data."*

Equally gratifying are the results from the randomized clinical trial of our digital intervention platform for depression supported by NIMH SBIR funding. In that study, we demonstrated that our behavioral inferences can form the basis of an efficacious digital intervention (See Frank et al, <https://pubmed.ncbi.nlm.nih.gov/36120713/>). In that study, our digital intervention platform for depression was associated with significantly greater improvement in depressive symptoms in psychiatric outpatients (simultaneously receiving standard of care outpatient treatment including antidepressant pharmacotherapy provided by academic faculty psychiatrists) who entered the trial in a moderately severe to severe depressive episode than that observed in the control condition consisting of standard of care outpatient treatment only. This innovation represents one of the only studies in the literature demonstrating the ability of any behavioral intervention, face-to-face or digital, to add significantly to well done pharmacotherapy for depression. Of note, unlike most other digital interventions, sustained adherence to the Cue platform was remarkably high. Of the 133 patients entered into the 16-week trial, only 10 discontinued the treatment, for a sustained engagement rate of 92%

Finally, working with UCHHealth, a highly innovative digitally sophisticated health system, we have already begun to see the potential of combining Cue's measurement capabilities with a 24/7 behavioral care response team to short-circuit impending mental health crises through very early detection and immediate intervention. This 24/7 approach to measurement enabled the detection of suicidality with plan that had gone undetected by the patient's provider and in another patient, the identification of a new episode of mania within four days of the onset of symptoms that would also have gone undetected given the patient's usual cadence of clinical visits.

Future research opportunities:

The introduction of the concept of passively acquired Behavioral Vital Signs has the potential to dramatically change psychiatric medicine in ways similar to what has occurred with the development of continuous, objective measurement for diabetes or heart disease. By employing algorithms that exploit the scientifically established significance of physiological and behavioral rhythms in disease progression, these tools can generate patient-specific digital biomarkers. As we note above, such biomarkers, in turn, can inform patient-specific interventions, enabling psychiatric medicine to move in the direction of true personalized medicine.

Our health system and pharmaceutical company collaborators also clearly see the value that HealthRhythms' Cue platform can create. Richard Zane, Chair of Emergency Medicine at the University of Colorado School of Medicine and Chief Innovation Officer for UCH said, *"As you know, you can kiss a lot of frogs in the digital health space. In the behavioral health digital health space, I think we've kissed every tadpole and every frog that exists. HealthRhythms was unique by orders of magnitude compared to any other company at which we looked. We had looked at probably 60 companies in this space. There's a number of unique things here - HealthRhythms' body of evidence to support their technology is robust. It's not a supposition or a hypothesis. It's established science."*

Our collaborators at Otsuka are equally enthusiastic. John Kraus, CMO and Jeff Weness, Head of Digital Opportunities and Investments, after having screened more than 500 digital

health solutions to bring just three to their sixth and final round of due diligence, made the following comment about their investment in HealthRhythms, *“We believe that the precision application of actionable data-driven insights in healthcare will transform how we serve patients in the coming decades. The partnership with HealthRhythms holds the potential to revolutionize how we approach R&D and commercialization of new mental health therapies by adding insights and precision never before available. Today we lack real insights into how our patients fare between treatments. With HealthRhythms. we hope to gain the insights critical to helping patients progress toward sustained mental health.”*

To date, HealthRhythms’ research has focused on psychiatric patients and primarily on those with mood and anxiety disorders and schizophrenia, but the implications for future research in three areas are enormous. First, we naturally plan to expand our portfolio to include a much **broader range of psychiatric and neurologic conditions** including attention deficit disorder, post-traumatic stress disorder, sleep-wake disorders, eating disorders, early dementias, multiple sclerosis, and Parkinson’s disease.

Second, it is clear that when **mood or anxiety symptoms are present as co-morbid conditions** with virtually any chronic illness, including diabetes, cardiovascular disease and many cancers, the costs of care increases dramatically, and treatment outcomes are consistently worse. We are about to begin programs in chronic disease patients using Cue to identify co-morbid depression and anxiety and, once treatment of the depression or anxiety is initiated, monitor treatment efficacy. We hypothesize that early identification and successful treatment of these co-morbid psychiatric conditions should significantly improve chronic disease outcomes while also significantly reducing costs of care.

Third, in the decades since the first delineation of the social zeitgeber hypothesis, there has been an explosion of research on the **relevance of circadian factors to a broad range of diseases** from cancers to endocrine disorders to cardiovascular disease to obesity. Indeed, it would appear that circadian factors are relevant to virtually every disease in which inflammatory processes are implicated. We envision a role for Cue in assessing the extent of social rhythm dysregulation chronic disease patients are experiencing and, where indicated, in providing digital

intervention to increase social rhythm regularity with the goal of indirectly improving disease trajectories.

HealthRhythms' potential to improve the human condition

The human condition is deeply and tragically affected by mental disorders and by mood disorders in particular. Since the year 2000, the World Health Organization has consistently ranked depressive disorders among the top 20 causes of Disability Adjusted Life Years (DALY's) worldwide. In their groundbreaking 1996 paper, Murray & Lopez demonstrated the enormous burden that unipolar depressive disorders place on society, then ranking depressive disorders as the fourth leading cause of burden among all diseases. They reported that depression accounted for 3.7% of total disability-adjusted life-years (DALYs) and was one of the leading causes of years lived with disability (YLD), accounting for 10.7% of total YLDs.

Below we provide just two examples of how such global prevalence statistics fail to capture the full impact of mental disorders on the human condition and the potential of HealthRhythms' Cue platform to mitigate the suffering associated with depression and other mental disorders.

The impact of maternal depression on offspring. As Üstün and colleagues pointed out in their 2004 paper, what the WHO figures do not account for is the fact that the burden of depression disproportionately falls on women, leading to ripple effects on those in the woman's family circle particularly her children. In the last two decades, a wide range of studies have demonstrated that the impact of depression in mothers on infants and young children has enduring effects on the social, emotional, and physiologic development of their children. Thus, the burden of depression disorders falls not just on the woman with the disorder but on her offspring and not just while the depression persists, but long into the future of her children.

Consequences of maternal depression in the **prenatal period** include higher rates of preterm birth, low birth weight, pre-eclampsia and spontaneous abortion. Studies of the **infants** of depressed mothers indicate deficits in the infant's self-regulatory behavior and dysregulated attention and arousal and lower cognitive performance compared to matched infants whose mothers were not depressed during pregnancy or the postpartum. Even if the depressed mother recovers from her depression, the multiple impacts on her child's development persist into the

toddler, preschool, school age and adolescent years, with increased behavior problems and cognitive impairments that lead to lower academic performance compared to the children of mothers who did not suffer from depression.

These relationships are unquestionably complex and multi-determined including physiologic factors during pregnancy, genetic factors, and behavioral factors. However, there is clear reason to believe that appropriate diagnosis and efficacious treatment of the mother's depression, especially during pregnancy and postpartum could mitigate many of these problems. Our platform, when embedded in a health systems' patient experience app provides the hope of early identification of maternal depression. Once she is engaged in treatment our platform can assess the efficacy of that treatment and guide the provider to an optimal outcome for the mother which, in turn, has the potential to change the lives of her children.

Years lost to missed diagnosis of bipolar disorder. Another example of how our technology can potentially change the lives of individuals with mental disorders comes from multiple studies indicating that the time from first clinical contact to a correct diagnosis of bipolar disorder is approximately ten years. This is at least partially because the typical individual with bipolar disorder experiences several episodes of depression before their first episode of mania. Those ten years of missed diagnosis often occur in the period between adolescence and early adulthood, a time when undiagnosed illness means critical development in social relationships may fail to occur and educational attainment that determines subsequent life trajectories is not achieved.

If young people with unrecognized bipolar disorder do come to clinical attention, it is typically when they are depressed. The clinician sees someone with the criterion symptoms of major depression and treats accordingly. Unfortunately, the typical treatment approaches for unipolar depression do nothing to prevent the onset of subsequent mania and, in some cases, can actually worsen the course illness. Retrospective reports of young adults ultimately diagnosed with bipolar disorder provide rich insights into their pre-diagnosis behavior which suggest that many of the behavioral inferences we have developed could provide the early detection and correct diagnosis that might have altered the trajectory of these individual's lives.

Based on these insights, we are currently working on models to detect unrecognized incipient bipolar disorder early in the course of illness so that appropriate treatment can be provided, and critical years of optimal functioning are not lost.

Summary: the promise of HealthRhythms' technology

The Cue platform holds the promise of **scalable, objective measurement** of depression risk and symptom severity for virtually anyone among the world's over 7 billion smartphone users regardless of their age or gender. With that promise comes the possibility of early intervention to short circuit months and even years of suffering from untreated disorder and the reduction of the collateral effects on the suffering on family members, especially the children of the depressed individual. It also brings the critical ability to **measure the efficacy of intervention objectively**, whether that intervention is a group psychotherapy provided by trained community therapists in Uganda or a state-of-the-art pharmacotherapy offered in New York, London, Paris, or Tokyo. And it holds the promise of an **efficacious, scalable digital intervention** that can begin to address the crisis in mental health treatment access.

Finally, we know that depression and anxiety disorders, even subsyndromal presentations of these conditions, have a powerful negative impact on the course of chronic illnesses such as diabetes, cardiovascular disease, multiple sclerosis, and Parkinson's disease. The identification of such depressive conditions through effortless continuous and objective measurement in the context of chronic illness holds the promise of **significant improvement in the course of the chronic illness, significant improvement in patients' quality of life along with significant decreases in the excess cost of care** attributable to the psychiatric co-morbidity.

HealthRhythms is on a clear path to realizing each of these promises and is fully committed to doing so.