

HealthRhythms: History of the Development of the Cue Platform

Our path to the development of the Cue platform began with a conceptual model of mood disorders that two of HealthRhythms' co-founders (Ellen Frank and David Kupfer) articulated as early as 1988: the *social zeitgeber hypothesis* of mood disorders. We argued that challenges to the body's circadian system are at the center of many of the disturbances (i.e., criterion symptoms) seen in mood disorders. Furthermore, such challenges are often a function of social role demands such as caring for children or employment that are important determinants of a person's daily routines. While regularity of daily routines such as the timing of sleep, activity, meals, and interpersonal contact could support a healthy circadian system, irregularity of these routines could challenge circadian rhythmicity, triggering new episodes of illness or serving as a factor in maintaining the mood disturbance. This conceptual model undergirds both HealthRhythms' measurement and assessment as well as our digital intervention technology. Thus, understanding and supporting the health of the circadian system as influenced by our behavioral routines can be thought of as the *mechanism of action* of HealthRhythms' Cue platform.

In the 1990's, Drs. Frank, Kupfer and colleagues developed a now widely used self-report instrument, the Social Rhythm Metric, to assess these daily routines or 'social rhythms,' but recognized that long-term adherence to its daily completion requirement was an unreasonable expectation. A decade later, Dr. Frank developed and validated a face-to-face intervention, Interpersonal and Social Rhythm Therapy, for individuals with bipolar disorder but the challenge of training a sufficient cohort of therapists to meet the need for this treatment meant that it was not scalable.

Beginning with the availability of the crudest flip phones, our co-founders began to explore the potential of these intimate devices as a way of obtaining a fuller understanding of the psychiatric patient's experience. Dr. Matthews began his research in the field back in 2002 and developed the very first mobile phone (i.e. pre-smartphone) application for children and teenagers with anxiety and depression, presenting this information to clinicians for the very first

time within their workflows. This early work was critical in helping us to understand that any provider-facing technology we built had to fit seamlessly into the provider's workflow and, if possible, lead to what some refer to as 'negative work.'

Once sensors became an integral feature of cellular phones, our co-founders immediately understood the enormous potential of these devices to create a 24/7 window into health-relevant behaviors. More than 15 years ago, Drs. Choudhury and Matthews pioneered digital phenotyping in consumer devices via the passive detection and analysis of voice, physical activity, technology use and social activity, all notably in behavioral health including in the areas of bipolar disorder, depression, and schizophrenia. An illustrative example is co-founder Choudhury's 2006 academic paper that identified a system for classifying physical activities (e.g., walking, running) many years before this approach became the standard on iOS, Android smartphones or on wearables like Fitbit. This breakthrough was recognized with a 10-year impact award by the premier conference in this space, Ubicomp in 2016. Again, this work that preceded the founding of HealthRhythms informed the kind of technology we have developed and the specific kinds of inferences about patient behavior we have created.

When Drs. Matthews and Choudhury were introduced to Drs. Frank and Kupfer, we had already realized that the commercial smartphone had the potential to meet both the objective measurement and the access deficits that were plaguing psychiatric care. Indeed, the smartphone seemed purpose built for those objectives, particularly when operating from a social rhythm regulation model. All that was needed was to meld Drs. Matthews and Choudhury's technical expertise and experience with Drs. Frank and Kupfer's clinical expertise and experience. Doing so has enabled HealthRhythms to capitalize on what the smartphone is capable of while understanding the needs of the patients who would ultimately benefit from our platform. For example, recognizing that individuals with mental disorders were likely to be especially privacy sensitive we have developed and registered a method for obfuscating the user's actual home location (*Method and System of Obfuscating Digital Location Data*, Attorney Docket No. 089664.0119), while maintaining the ability to 'sense' the user's time spent at home, the timing and number of entrances and exits from home, the number of novel locations visited and the distances traveled from home all of which are important markers of patients' clinical status.

HealthRhythms' efforts to develop and validate the Cue platform were initially supported with Small Business Innovation Research (SBIR) funding from the National Institute of Mental Health and the National Institute on Alcohol Abuse and Alcoholism and, subsequently, with seed funding from a remarkable cohort of 44 health tech investors and category pioneers, enabling us to raise \$11m in venture capital, in addition to the \$7m of non-dilutive funding we had raised from the National Institutes of Health. Our recently concluded successful A round of funding (\$22m) includes support from an equally remarkable group of investors, including a second \$3m investment from University of Colorado's CU Innovations and an additional \$3m from Otsuka.