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Towards precision clinical trials and personalized prevention in CHR with smartphone digital phenotyping and personal sensing tools.

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Smartphone digital phenotyping, also known as personal sensing (Mohr et al, 2020), offers an accessible and scalable means to deliver precision mental health across all conditions – but holds a high potential for those with clinical high risk (CHR) for psychosis. This population's enriched use of smartphone technology, precise measurements offered via digital phenotyping, and adaptive treatments offered via apps, creates an actionable framework for precision clinical trials (Lenze et al, 2020) and personalized prevention desperately needed-yet currently remains underutilized.

Digital phenotyping offers a valuable approach for CHR research and care delivery given the near ubiquitous smartphone ownership by youth and increased reliance on mobile devices for daily functioning. While CHR specific data on smartphone access is scarce, early course psychosis patients have high rates of ownership (Camacho et al, 2019) in line with national findings for youth-above 90%. Youth today use their smartphones as the primary means of accessing the internet for communicating with friends, ordering food, doing shopping, and accessing transportation is rising. In seeking to understand how the current generation of youth behave and how the CHR status can impact functioning and thriving, not looking through the lens of their smartphones is ignoring the reality and influence of the online world.

Smartphones are also the right tool for CHR research and care delivery given their ability to capture the real-time, dynamic, and longitudinal experiences of individuals across symptoms, behavioral, and physiological domains. Monitoring CHR patients' symptoms via smartphone surveys was first done in 2012 and demonstrated high internal consistency and sensitivity to clinically reported change (Palmier-Claus et al, 2012). There is however less research on understanding CHR patients' behaviors and physiology through smartphone digital phenotyping. A 2018 study collected smartphone digital phenotyping from 12 CHR individuals (Niendam et al, 2018) and demonstrated feasibility but did not report on sensor

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driven outcomes. A 2019 study in early course psychosis utilized a smartphone app and wearable sensor to show that those with increased hallucinations and delusions had significantly higher electrodermal activity levels (Cella et al, 2019) – highlighting the potential for CHR as do a growing number of digital phenotyping studies in psychosis. The potential of this approach is especially relevant for CHR as in seeking to predict risk of conversion and means of prevention, smartphones can gather novel environmental data, (e.g. greenspace exposure and air quality) simply non-obtainable at scale for each individual via other methods, and create dynamic risk models that are personalized to each individual– not just populations.

Smartphones are finally the right tool for CHR research and care delivery because they can interpret and act on data to offer just-in-time adaptive interventions that increase access to care. The potential of any risk score or clinical insight into a CHR patient's status is only as useful as it can help that patient reduce risk and improve their state. A growing literature on smartphone apps offering interventions specifically for CHR highlights that even today these tools can be engaging and effective (Camacho et al, 2018. Yet most current CHR app interventions are not designed to be just-in-time, meaning that they do not respond to real-time risks or offer in the moment support. An expanding body of literature suggests that to drive sustained engagement, apps must be personalized and offer customized resources – an important target for the next generation of digital CHR interventions.

Beyond creating a framework for precision mental health for CHR, smartphone digital phenotyping offers a pathway to uncover mechanistic understanding and develop new treatments that will deliver greater impact than any app intervention today can. Considering how smartphone surveys and digital phenotyping can offer data across the National Institute of Mental Health's Research Domain Criteria' (RDoC) units of analysis including self-report, behavior, and physiology-these digital signals can serve as a dynamic and new multi-modal bridge to connect genes, molecules, cells, and circuits (Torous et al, 2017) The foundation of this bridge will be statistical methods and machine learning (ML) approaches which today have been deployed on this type of data but rarely at scale or with appropriate sample sizes (Barnett et al, 2018) – and not yet in CHR. Analysis of language based markers as predictors of outcome in CHR (Bedi et al, 2015) which can be developed as smartphone based digital phenotypic measures, is a good example of potential future directions in this field. With such novel data captured and analytic methods in place, the potential to link psychiatry with neuroscience and biology offers unique potential in moving CHR towards prevention and new mechanistic understanding of risk progression and conversion.

This potential however belies the challenges in using mobile technology to advance care for CHR. The high heterogenicity in models of smartphones owned as well as device variance in terms of sensors and ability to run apps must be accounted for (Torous et al, 2018). A further limitation is that signals may be small and require larger samples to accurately tease out noise. Finally, the ability to offer app interventions does not forgo the need for face-to-face care and the strongest evidence today for app use suggests a blended approach with human interaction supporting technology. While these challenges cannot be ignored – they can be solved. Large consortia bringing together diverse CHR patients in appropriate sample sizes can embrace device and sensor heterogeneity with statistical power to identity signals. These

consortia can use the diversity of CHR patients and teams to also harmonize implementation and engagement efforts to ensure new tools are ethically, culturally, and clinically appropriate. Linking the digital efforts of these consortia to their ongoing biological and neuroscience research will ensure the highest potential of this approach can be realized.

Precision clinical trials and personalized prevention for CHR are possible, and smartphone tools like digital phenotyping offer an actionable, low-cost, highly scalable and 'shovel ready' avenue for further exploration. The ability to advance CHR care today through research advancing personalized prediction and just-in-time adaptive interventions is buttressed by the potential to advance mechanistic understanding to deliver personalized prevention tomorrow.

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