

## **Ethical Issues in Psychosis Screening and Prevention**

Cheryl Corcoran MD  
Yulia Landa PhD  
Icahn School of Medicine at Mount Sinai,  
New York, NY, USA

### **Introduction**

Psychotic disorders such as schizophrenia are among the leading causes of disability worldwide, especially in developed countries (Lopez, Mathers, Ezzati, Jamison, & Murray, 2006). Psychotic disorders typically have their onset in adolescence and young adulthood, and are lifelong chronic illnesses that are managed with psychopharmacological and psychosocial interventions. While some individuals have a remission of illness, and many more achieve recovery, there remain a substantial proportion who have persistent morbidity related to accompanying cognitive deficits and negative symptoms (impairments in motivation and expression) that interfere with social and vocational function. Hence, there has been a worldwide effort over the past few decades to identify young people during a putative prodromal phase of illness, who have attenuated or subthreshold psychotic symptoms, in order to develop early preventive interventions before an index episode of psychosis. This enterprise has had some success in beginning to clarify the neural basis of the emergence of schizophrenia and related psychotic disorders, which is important for the work that remains to be done in identifying targets for intervention. However, in respect to public health, this research has not yet led to a reduction in the incidence of schizophrenia and related psychotic disorders.

### **The clinical or ultra-high risk (CHR/UHR) paradigm**

The implementation of the clinical or ultra-high risk (CHR/UHR) paradigm for early detection and prevention in psychotic disorders such as schizophrenia began in earnest in the 1990s (Miller et al., 1999), motivated by the impetus to prevent the significant morbidity associated with these

chronic illnesses. There were a few main sources of inspiration for this endeavor. First, retrospective studies (Hafner et al., 1998; Walker & Lewine, 1990) demonstrated that there were early behavioral markers of later psychotic illness, including social withdrawal, anxiety, unusual thoughts, suspiciousness, slow functional decline, and motor disturbances; hence, individuals at risk could be identified. Second, there was the introduction of atypical second-generation antipsychotics (Opjordsmoen et al., 2009), which seemed safer to administer even to young people at risk, as they were not associated with the disfiguring adverse effects of tardive dyskinesia; reflecting this, among the earliest CHR/UHR research studies were randomized clinical trials that included second generation antipsychotics (SGA's) (McGlashan et al., 2006).

### **Advances in research on prodromal schizophrenia: putative biomarkers**

When we first started doing clinical high-risk research two decades ago, publications on CHR/UHR were rare enough that we would print them and add them to our binders of manuscripts. Now this would be an exercise in futility, given the explosion in this area of research. Despite contrary arguments by some of our colleagues (van Os & Guloksuz, 2017), we would argue that this area of research has come a long way in the behavioral phenotyping of the putative schizophrenia prodrome and in the identification of promising replicated biomarkers that shed light on the early pre-psychotic stages of schizophrenia and related psychotic disorders. For instance, disturbances in language production (Bearden, Wu, Caplan, & Cannon, 2011; Bedi, 2015; DeVylder et al., 2014b), as measured using clinical rating scales such as the Scale of Prodromal Syndromes/Scale of Prodromal Symptoms (SIPS/SOPS) (Miller et al., 1999), is a replicated behavioral risk factor for psychosis onset among CHR/UHR individuals that is now studied using automated linguistic analyses (Bedi, 2015), finding reductions in semantic coherence and syntactic complexity as early pre-psychosis markers of emergent schizophrenia. Related to this, deficits in verbal fluency, verbal memory, and processing speed – all relevant for language – are also replicated risk biomarkers of psychosis onset among CHR/UHR youths (Addington et al., 2017). In the realm of sensory processing, a reduction in amplitude to deviant auditory stimuli, as measured with EEG, in the auditory oddball mismatch paradigm has now been replicated in multiple studies as a predictor of psychosis onset among CHR/UHR youths (Bodatsch et al., 2011; Kayser et al., 2014; Perez et al., 2014; Shaikh et al., 2012; van Tricht et al., 2015). And there are other replicated predictors of

psychosis onset, including reduction in gray matter (Chung et al., 2017), particularly in limbic regions such as the hippocampus (Schobel et al., 2013), as well as abnormal patterns of resting state functional connectivity (Anticevic et al., 2015; Colibazzi et al., 2017) and patterns of proinflammatory cytokine expression (Zheutlin et al., 2017). The task remains to integrate these varied but replicated findings, much as the blind men in the parable had to reconcile that a snakelike trunk, a ropelike tail, a spear-like tusk, fanlike ears, and legs like tree trunks altogether comprise an elephant.

### **Advances in research on prodromal schizophrenia: potential treatments**

Beyond phenotypic characterization and the emergent study of putative risk biomarkers, CHR/UHR research has also focused on identifying effective interventions and treatments. Among the earliest of these were randomized clinical trials with second-generation antipsychotics. Some had efficacy and some did not, but overall, the side effect profiles tend to be unfavorable for these agents in at-risk youths who are more sensitive to side effects than adults, but who also as a group comprise “false positives” or individuals mistakenly identified as at risk. Other pharmacological agents have been tested with no clear signal of efficacy for any of these yet. Omega fatty acids looked promising in initial studies (Amminger et al., 2010), but their efficacy was not replicated (McGorry et al., 2017). D-serine can improve negative symptoms but does not seem to prevent psychosis (Kantrowitz et al., 2015). Among the more promising treatments thus far are non-pharmacological treatments, including cognitive behavioral therapy (Fusar-Poli, Bonoldi, et al., 2012; Ising et al., 2016) and cognitive remediation (Choi et al., 2017), which have both efficacy and a minimum of side effects. Trials are just beginning for non-invasive brain stimulation strategies, which may have promise for improving cognitive deficits in risk states for psychosis.

The strength of these efforts lies in the reliable and accurate diagnostic methods we have for case identification, as the CHR/UHR syndrome is determined by the nearly universal use of two similar gold-standard measures - the SIPS/SOPS (Miller et al., 1999) and the Comprehensive Assessment of At-Risk Mental States (CAARMS) (Yung et al., 2005). With the use of these measures, and similar recruitment and ascertainment strategies across sites, and especially with the existence of consortia, in fact CHR/UHR cohorts are remarkably similar worldwide, with mean age in the late teens/early twenties, a preponderance of males, similar comorbidity with prevalent cannabis

use, prevalent negative symptoms, and a profile of mild to moderate cognitive deficits across domains (Fusar-Poli, Deste, et al., 2012). With the relative consistency in case identification worldwide, we have begun to identify and replicate promising biomarkers and interventions which, in the future, we will increasingly put together in studies.

### **Ethical issues related to the psychosis risk paradigm: labeling and stigma**

In the past two decades, many clinicians and researchers have addressed the ethical issues inherent in the CHR/UHR clinical and research enterprise, and this reached critical mass when the attenuated psychotic symptom syndrome was considered for inclusion as a disorder in the 5<sup>th</sup> edition of the Diagnostic and Statistical Manual (DSM-5). In respect to beneficence, it was rightly argued that the identification of young people with attenuated psychotic symptoms who were symptomatic and help-seeking would lead to treatment of their current symptoms, which can include depression, anxiety, and functional impairment, and overall reduce duration of untreated symptoms and improve course, perhaps even preventing psychosis onset in some individuals (Woods, Walsh, Saks, & McGlashan, 2010).

However, concerns were raised about the high false-positive rate in respect to psychosis risk, as the majority of young people who were ascertained as at risk, even in tertiary care specialized centers, would not develop psychosis in the ensuing years (Corcoran, First, & Cornblatt, 2010). Preliminary evidence suggested the false-positive rate would be even higher in the community, not so much because community clinicians lacked specific expertise and experience in determining psychosis risk, but because base rates of the psychosis risk syndrome are low (Yung et al., 2008). This has since been confirmed by Fusar-Poli and colleagues, who have shown that “risk enrichment” in a community sample is low, as compared with cohorts ascertained through orchestrated recruitment and outreach strategies (Fusar-Poli et al., 2016). But even in tertiary care specialty programs, the false positive rate exceeds sixty percent (DeVylder et al., 2014a; Fusar-Poli, Bonoldi, et al., 2012). High false-positive rates are not problematic in and of themselves, if the risk-benefit ratio is favorable, as it is for screening for cardiovascular risk factors. However, there was concern about the risk of unnecessary exposure to antipsychotic medications in young people, as well as the risk of stigma and discrimination. Given this, the Attenuated Psychosis Syndrome (APS) was

included in the appendix of the DSM-5 as a syndrome requiring further study (Corcoran et al., 2010).

More recent research suggests that CHR youth associate more stigma with their symptoms and with the negative response of others to their odd behaviors, than they do with at-risk label itself (Yang et al., 2015). Information about CHR status, when sensitively delivered, could promote autonomy, help clarify and/or correct previous diagnoses, and facilitate treatment engagement (Mittal, Dean, Mittal, & Saks, 2015). Moreover, our findings from a series of qualitative studies suggest that patients and caregivers want to have direct and accurate information about their diagnosis, including the diagnosis of psychosis-risk and schizophrenia when appropriate (Loughland, Cheng, et al., 2015; Loughland, Kelly, et al., 2015; Outram, Harris, Kelly, Bylund, et al., 2015; Outram, Harris, Kelly, Cohen, et al., 2015; Outram et al., 2014). Thus, we conducted interviews with patients who were given a diagnosis and their caregivers, as well as with clinicians who provided such diagnostic information. One of the major themes identified pertained to delays in receiving correct information about diagnosis, and related delays in finding appropriate care (Loughland, Cheng, et al., 2015; Outram, Harris, Kelly, Bylund, et al., 2015). A primary reason cited by clinicians for not providing a diagnosis was diagnostic uncertainty, as well as concerns about distress and stigma that might accompany providing a diagnosis (Outram et al., 2014). But a case register study from Denmark showed that while persons who were initially given a correct diagnosis of schizophrenia had longer first hospital admissions, they had fewer subsequent hospitalizations as compared with individuals who were not initially diagnosed but later received a diagnosis of schizophrenia (Munkjorgensen, Mortensen, & Machon, 1991). These findings suggest that recognition and accurate diagnosis of psychosis-risk and psychosis, as well as open communication between clinicians and patients about psychotic symptoms, are beneficial and do not cause harm.

Thus, the risk/benefit ratio may have tipped toward reifying the APS as a syndrome in and of itself that simply warrants treatment, with the current evidence favoring psychological treatments such as cognitive behavioral therapy and cognitive remediation, which respectively improve the symptoms and cognitive deficits that impair concurrent function. Functional impairment is common among individuals with APS, even among those who do not transition to psychosis in the near term of three to five years, supporting that this syndrome is clinically relevant even apart from its associated psychosis risk (Carrion et al., 2013). Meta-analyses of transition outcomes in at-risk individuals (Fusar-Poli et al., 2012) suggest that cognitive behavioral therapy (CBT) may reduce the

risk of transition to psychosis; this protective effect has been shown to last up to four years (Ising et al., 2016). Even if these treatments only delayed psychosis onset, this would still confer benefits, as it would enable young people to further consolidate academic achievement and social networks. Monitoring individuals at risk for psychosis can also minimize delays in referral to stage-specific care in those individuals who develop psychosis, reducing duration of untreated psychosis and potentially improving course of illness (Amminger et al., 2011; Barnes et al., 2008).

### **Ethical issues related to the psychosis risk paradigm: A public health perspective**

But beyond the ethical issues inherent in clinical high-risk intervention and research, primarily in respect to the risk label itself and its potential beneficial and negative effects, there are also ethical and practical issues as to whether this strategy is the best use of limited resources. That is, from a public health perspective, what percentage of early schizophrenia cases are we capturing for evaluation and treatment - or missing entirely - using a tertiary specialty clinical high-risk early identification paradigm? The issue is not simply false positives, but the sensitivity of the CHR/UHR approach at the population level.

In a novel clinical register-based cohort study in South London of patients in secondary mental health services, the CHR/UHR designation captured only 52 of the 1001 patients who converted or made a transition to psychosis over six years; this represents a sensitivity of only 5.2%, even though the neighboring Outreach and Support in South London (OASIS) program is a well-established specialty CHR/UHR program in the South London area with impressive resources for outreach (Fusar-Poli et al., 2017). None of the other 94.8% who developed psychosis outside of OASIS had been screened for attenuated psychotic symptoms, such that some of what might account for the low sensitivity of the CHR/UHR designation was that it was not considered or utilized outside of specialty services. However, a Clinical Record Interactive Search (CRIS) tool was used to search and retrieve data from the electronic medical records in order to identify predictors of (and hazards for) psychosis onset beyond CHR/UHR status gleaned from individual records of routine mental health care, comprising hypothesized demographic and clinical measures easily collected in the clinic. The predictors tested were circumscribed to diagnosis and demographic variables such as age, gender, and ethnicity; not surprisingly, the authors found significantly increased hazard for age,



male sex, all categories of nonwhite ethnicity, and acute and transient psychotic disorder and bipolar disorder. The model had good to strong predictive accuracy using the Harrell's C statistic for proportional hazards analysis. Overall, the risk of psychosis among these patients in secondary mental health services was fivefold that in the local general population, suggesting that receiving psychiatric care is relatively sensitive (though certainly not specific) to capturing psychosis, though the exact sensitivity cannot be calculated absent the denominator of the size of the local general population.

### **Future directions: the use of artificial intelligence in prediction**

This initial electronic medical record study in South London (Fusar-Poli et al., 2017) is quite promising and is a good first step. However, the menu of predictors considered was limited, consisting only of diagnosis and demographics, with the authors providing a rationale for predictor selection based on "clinical knowledge and previous studies." Further, the risk in this hypothesis-driven approach is that extant predictors or hazards not previously considered or hypothesized will be missed. An alternative approach is to use natural language processing strategies to extract data from electronic medical records, in conjunction with machine learning (Wang et al., 2017), to identify patterns and phenotypes that distinguish conversion to psychosis: this would likely identify latent aspects of emergent psychosis that we have not yet considered. We have applied this strategy of natural language processing with machine learning to speech transcripts obtained from youths identified as CHR/UHR for psychosis, finding semantic and syntactic features reflective of language disturbance to predict psychosis onset (Bedi, 2015). This same strategy, albeit with a focus on the content of language, rather than its structure, could be used to evaluate the text and language of clinicians caring for patients for its prognostic value in respect to psychosis.

The application of natural language processing analyses with machine learning to big data sets, specifically electronic medical records in primary care or general psychiatric services, holds promise for the broader identification of individuals at risk for psychosis beyond the tertiary care CHR/UHR paradigm, and is relatively inexpensive to utilize once the data analytic programs are built and established. This may help us optimize the use of limited resources in our efforts to truly prevent schizophrenia. Nonetheless, these approaches raise other ethical issues that demand our attention,

specifically the protection of privacy for patients and keeping their medical records confidential (Wang et al., 2017). The prospect of mining of medical records will require its own ethical cost/benefit analysis. Further, improvement in prediction at the clinic or population level requires that appropriate evidence-based treatments exist for individuals identified, and that they are accessible. Currently, some of the most promising treatments available are also portable and can be delivered via the internet, including cognitive behavioral therapy and cognitive remediation.

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Address for correspondence: e-mail: [cheryl.corcoran@mssm.edu](mailto:cheryl.corcoran@mssm.edu)

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