

# Identifying Vulnerability Markers in Prodromal Patients: A Step in the Right Direction for Schizophrenia Prevention

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## FOCUS POINTS

- How could the identification of prodromal markers lead to the development of neuroprotective therapies?
- Evaluate the beneficial and detrimental effects associated with including attenuated negative and disorganised symptoms in prodromal criteria.
- Would the identification of prodromal markers provide support for the neurodevelopmental or neurodegenerative theory of schizophrenia?
- What are the ethical implications of exposing someone to antipsychotic therapy given that they may not develop schizophrenia or even psychosis?

## ABSTRACT

Research has shown that many of the long-term deficits that are observable in schizophrenia populations are present prior to the emergence of psychotic symptoms. Recent research suggests schizophrenia has a “prodromal” period, whereby significant changes from premorbid functioning can be observed. Accurate classification of this period could have far-reaching implications for schizophrenia prevention. This article aims to provide an indepth evaluation of the perceived benefits of vulnerability marker research in this unique phase. It is hoped that identification of such markers may improve the predictive potency of prodromal criteria, and perhaps pave the way for future screening and primary prevention strategies.

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## INTRODUCTION

Since Kraepelin’s times, schizophrenia has been viewed as a disorder with an inevitable, severe, and debilitating course. Epidemiological studies and public health reports exemplify this with a world-

wide prevalence of ~1%.<sup>1</sup> In addition, The Global Burden of Disease Report (1996) reveals that schizophrenia features in the top-10 contributors to health burden, therefore, constituting a large proportion of disability around the world.<sup>2</sup> Such a bleak picture is accentuated by the findings of Hagarty and colleagues,<sup>3</sup> who conclude that current treatments for schizophrenia remain essentially palliative and have not moved forwards in terms of functional outcome in the last 100 years.

The idea that intervention in the early phases of psychotic illness may improve prognosis for both patients and their caregivers was first postulated by Sullivan in 1927,<sup>4</sup> and echoed in later years.<sup>5,6</sup> Subsequent findings from early first episode work in the mid-1980s lends further support to this hypothesis.<sup>7,8</sup> However, work in early psychosis did not begin until the 1990s, with the publication of several key research studies.<sup>9-12</sup> The findings of these studies highlights the special requirements of young people with early psychosis. This growing body of evidence is further supported by the finding that the earlier antipsychotic medications are administered after the onset of psychosis, the better the outcome.<sup>13-18</sup> The notion that the longer psychosis remains untreated, the poorer the prognosis, is typically referred to as the duration of untreated psychosis effect.

It is these advances, combined with the development of newer antipsychotic medications with a better side-effect profile, that has made early psychosis a popular focus for those involved in schizophrenia research and treatment over the last few years.<sup>19</sup>

## EARLY INTERVENTION

During the 1980s, investigations consistently found that subtle changes in thought, affect, and behavior actually precede the development of acute

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psychosis.<sup>20-22</sup> This period was later identified as the schizophrenia prodrome, which is currently defined as the stage of schizophrenia that begins with the first changes in behaviour and lasts up until the onset of psychosis.<sup>23-25</sup> The prodromal stage of schizophrenia, therefore, differs from the premorbid stage in the following way: the prodrome represents the attainment of a “threshold level” whereby underlying pathological processes become expressed as subthreshold psychotic symptoms (Figure).<sup>26</sup>

With the recognition of the prodromal phase of psychosis, combined with the aforementioned investigations which found a link between outcome and duration of untreated psychosis, fresh hope has grown for many researchers in the field, in that by treating psychosis prior to onset (ie, in the prodromal phases), the processes of illness development could be attenuated in such a way as to dramatically improve the prognosis of the disease. This has led to a dramatic shift of interest to the prodromal phase of schizophrenia.<sup>27,28</sup> Indeed, Yung and McGorry<sup>29</sup> note that the psychotic prodrome is potentially important for early diagnosis and management of psychotic disorders, early detection of relapse, prospective studies of high-risk individuals, and prognosis.

**Prevention Of Neurobiological Decline**

In addition to improving the prognosis of the disorder, it is hoped that by prospectively studying the early phases of psychotic disorders, researchers may gain insight into the neurobiological deficit

processes that are thought to be most active during this period.<sup>30,31</sup> This is consistent with the stress-vulnerability model of schizophrenia, which notes that during adolescence and early adulthood, previously masked vulnerability is revealed as deficit neurobiological processes, which are closely associated with the emergence of prodromal symptoms. By observing such deficit processes, the progressive psychobiological path from prodromal state to acute psychosis could, hopefully, be mapped. Indeed, the processes may be so far advanced by the time acute psychosis becomes apparent that chances of eventual recovery are minimal. Wyatt<sup>17</sup> goes one step further to suggest that active psychosis may be intrinsically neurobiologically toxic, adding to or accelerating the aforementioned neurobiological processes that lead to onset.

Hence by early intervention, such neurobiological processes may be manipulated and the resultant changes prevented.<sup>32</sup> Appropriate therapeutic intervention for such processes would be neuroprotective.

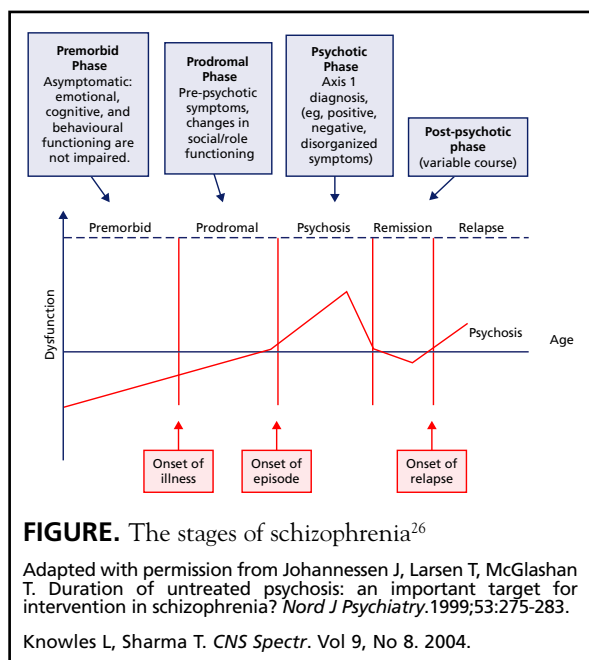
**Prevention Of Psychological And Social Decline**

The psychological and social effects of schizophrenia are profound, with individuals being plagued by a wide-range of problems when experiencing a first psychotic episode. This disruption is often compounded by the fact that age at onset of psychosis is typically late adolescence to early adulthood, a time of immense personal upheaval. At this time individuals typically enter a period of fear, hopelessness, powerlessness, and demoralisation, in addition to experiencing the damaging effects of stigmatisation, which has major adverse consequences within their social support network.

Hence, the aims of early intervention are to reduce the psychological, social, and biological aspects of disruption evident in the lead up to and expression of psychosis.<sup>33</sup> To achieve these aims, safe effective screening tools must be established. In order to identify such tools, accurate diagnostic mechanisms must also be readily available.

**CHARACTERIZING THE PRODROME**

The term “prodrome” is derived from the Greek word “prodromos”, meaning the forerunner of the event.<sup>34</sup> Many illnesses already have a well-established prodromal stage (eg, measles), and the term is traditionally used to describe the early signs and symptoms that precede the acute illness. Classification of the prodromal stage of psychosis has far-reaching implications for both service users and providers—in terms of early intervention, iden-



**FIGURE.** The stages of schizophrenia<sup>26</sup>  
 Adapted with permission from Johannessen J, Larsen T, McGlashan T. Duration of untreated psychosis: an important target for intervention in schizophrenia? *Nord J Psychiatry.* 1999;53:275-283.  
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tification of biological markers and understanding the process of becoming psychotic.

In order to treat individuals in the prodromal phase, defining criteria need to be met. To develop such diagnostic criteria, investigators need to look at existing prodromal cases. The problem therefore in defining prodromal criteria is that by nature, the term is retrospective. In order to truly describe a prodromal case, one would have to be convinced that the patient will go on to develop schizophrenia. Without accurate diagnostic criteria, such a prediction cannot be made. Hence, researchers are faced with a Catch-22, whereby the only place to start defining such a period would be to look at retrospective accounts. As pointed out by Yung and McGorry,<sup>29</sup> retrospective accounts of the psychotic prodrome are often subject to recall bias and “effort after meaning”. Furthermore, coping styles of patients and their carers may affect a retrospective description of the prodrome. Hence, criteria developed for this period are exploratory and constitute working definitions which are being modified and dictated by present day research. Indeed, in-depth investigations into this period have only been performed over the last 5 years and criteria vary significantly between different researchers.

One of the first widespread definitions of the schizophrenia prodrome intended for clinical diagnosis was published in *Diagnostic and Statistical Manual of Mental Disorders, Third Edition-Revised*.<sup>35</sup> Nine symptoms types were described, which include aspects such as blunted or inappropriate affect, markedly peculiar behavior and odd beliefs or magical thinking. Since these symptoms were first published, research has shown the criteria to be nonspecific,<sup>36</sup> and also question its predictive validity.<sup>25</sup> Häfner and colleagues<sup>37</sup> highlights the fact that this is a problem for all schizophrenia diagnostic criteria, since early symptoms are inherently nonspecific, which may explain why diagnosis is typically not made until several years after the development of the first symptom. Perhaps unsurprisingly then, the *Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition (DSM-IV)*<sup>38</sup> does not include the category for prodromal symptoms for schizophrenia.

Despite the aforementioned problems associated with retrospective research, Häfner and colleagues<sup>39</sup> have produced compelling findings from their retrospective studies. One published studies<sup>39</sup> found that 73% of first-episode patients experienced a prodromal phase that started with nonspecific prodromal signs (ie, depressed mood, anxiety, low self-esteem) or negative symptoms (ie, poor concentration, lack

of energy, worsening work performance), 20% with positive symptoms (ie, suspiciousness, perceptual abnormalities, disorganized thinking), and negative or nonspecific symptoms, and 7% with positive symptoms only. Such retrospective studies have provided many clues and established the framework for more recent, prospective research.

Recently, a large number of groups around the world have established prospective clinical programmes and carry out research focusing on early psychosis. Yung and McGorry<sup>29</sup> have developed the Personal Assessment and Crisis Evaluation (PACE) which has become a pioneering centre for prodromal research. They have developed a sophisticated “close-in” system of prospective diagnostic criteria. This constitutes of a multiple-gate screening mechanism which endeavours to minimize the number of false positives that were evident in older attempts to characterize an at-risk population.<sup>40</sup> The term “At Risk Mental State” (ARMS) is used to describe this population. Such labeling allows the definition to be a working model rather than an established diagnosis, hence to suggest an individual will develop schizophrenia if he or she meets ARMS criteria would be untrue. Instead the term conveys a heightened risk of schizophrenia rather than an early form of psychosis signalling an inevitable decline to schizophrenia.<sup>29</sup> Indeed, it is well known that certain recreational drug-use, stressful life events and conditions such as Wilson’s disease can induce symptoms similar to those seen in true prodromal patients. The diagnostic system delineates ARMS individuals into three categories of selection criteria<sup>41</sup>:

- Trait and State Risk Factor Group: Family history of psychotic illness or a *DSM-IV* schizotypal personality disorder and a recent change in mental state or;
- Attenuated Psychotic Symptoms Group: Subthreshold psychotic symptoms (such as unusual perceptual experiences) occurring several times a week over a period of at least 1 week or;
- Brief, Limited, or Intermittent Psychotic Symptoms Group: lasting less than 1 week and with spontaneous remission.

The above defined criteria are heavily reliant on positive symptoms of psychosis, despite much evidence suggesting that attenuated negative symptoms are also present in the prodromal stages of the illness.<sup>37,42-45</sup> Cornblatt and colleagues<sup>27</sup> argue that by omitting negative symptoms the McGorry ARMS definition effectively parallels criteria used to diagnose Axis I schizophrenia. However, McGorry and

colleagues<sup>29</sup> note that if nonspecific negative symptoms, such as depression, sleep disturbances, or anxiety, were included in their definition the number of false positives would be much greater, which is confirmed by earlier work.<sup>46,47</sup> Cornblatt and colleagues<sup>27</sup> do, however, use attenuated negative symptoms in their criteria, dividing their “clinical high risk” (CHR) group accordingly. Hence subjects experiencing attenuated negative or disorganized symptoms are classified as CHR negative (–), and subjects experiencing attenuated negative, disorganized and positive symptoms are classified as a separate clinical high-risk group, CHR positive (+). Cornblatt and colleagues<sup>27</sup> propose a developmental connection between the two groups, with the CHR– group representing early prodromal stages and the CHR+ group representing later prodromal stages, which is supported by other work.<sup>37,41,48</sup>

Researchers using the ARMS criteria report ~40% of individuals considered to be prodromal go on to become psychotic (NB, not necessarily schizophrenia).<sup>28,41,49,50</sup> This hit-rate has set the precedence for researchers using other prodromal diagnostic systems. It is worth noting that most groups limit the age of individuals entering the research programs to adolescence/early adulthood, since this is the age period established as having the most risk of developing psychosis.

### THE ISSUE OF PREDICTIVE ACCURACY

In spite of efforts to characterise the prodrome, >50% of cases defined as being at an elevated risk of developing psychosis will not go on to do so. As noted by Cook and Sackett<sup>51</sup> and Eaton and Harrison<sup>52</sup> in the development of their number needed to treat statistic, depending on the power and effectiveness of the treatment/intervention, number needed to treat to prevent one adverse outcome varies significantly. Reducing false positives is vital for prevention trials involving pharmacotherapy, especially when dealing with a young subject group.

The early phases of psychotic illnesses (ie, prodromal) need to be accurately classified in order to implement early intervention treatment programs and in turn improve prognosis. The identification of accurate risk factors or markers evident in the prodromal phase is critical to improve diagnostic accuracy. Indeed, Copolov and Crook<sup>53</sup> note that the delivery of biological markers for schizophrenia would greatly assist preventative strategies by identifying at-risk individuals who could then be monitored and treated in a manner to reduce subsequent

morbidity. This is the typical no-win situation of schizophrenia research. In the continuing absence of a robust biological marker, poorly defined criteria phenotypes impede the resultant search for a biological substrate. The heterogeneity of schizophrenia would imply that no one single specific marker exist. It is more likely that several factors interact to increase the individuals susceptibility to developing schizophrenia.

### THE SEARCH FOR RELIABLE MARKERS

#### *Traditional High-Risk Studies*

Traditional high-risk research in schizophrenia started in the 1950s and early 1960s. Such research typically focuses on identifying trait markers which are present in the healthy relatives of people diagnosed with schizophrenia and monitoring them over time.<sup>54-57</sup> The development of such genetic-high-risk (GHR) programs stems from the large body of evidence supporting a genetic component to schizophrenia. The risk of developing schizophrenia in family members increases with the degree of biological relatedness to the patient. Third-degree relatives (eg, first cousins) share ~12.5% of their genes. Hence, if one of these relatives is diagnosed with schizophrenia ~2% of their third-degree relatives will also develop schizophrenia. Similarly, second-degree relatives (eg, half siblings) share ~25% of their genes, and, accordingly, 6% of individuals with a diagnosed second-degree relative will develop schizophrenia. Most first-degree relatives (eg, siblings, dizygotic twins) share about 50% of their genes and as such ~9% of individuals with a first-degree relative with schizophrenia will develop schizophrenia. Monozygotic twins share 100% of their genes, which translates to a 50% risk of developing schizophrenia for one twin if the other is affected. There is a risk of 1% in the general population.<sup>58</sup>

By studying relatives of individuals diagnosed with schizophrenia, an enriched-risk group (in this case genetic) is identified. From this GHR group, additional risk factors which make the transition to a frank psychotic disorder more likely, can be examined. These studies tend to be long-term projects, which longitudinally follow high-risk individuals and control individuals from childhood or early adolescence, through to adulthood, thus covering the period of high risk (late adolescence and early adulthood).

One of the most well-replicated findings of GHR research<sup>59,60</sup> indicate subtle premorbid neurocognitive deficits may be markers of future illness. Many GHR studies include extensive neuropsychologi-

cal assessment. Typical findings<sup>59,60</sup> suggest specific deficits in attention and short-term memory may convey an increased risk of developing schizophrenia in those already at a genetic risk.

### **Limitations of Genetic High-Risk Research**

Although GHR studies have yielded some interesting findings, by definition only 9% of individuals with a first-degree relative who has a schizophrenia diagnosis can be expected to develop schizophrenia themselves. This, in turn, means that such projects have long latent periods, which means that such studies tend to become obsolete prior to their completion date. Hence, GHR projects invariably generate high costs, given their large scale, and are plagued by low positive predictive values. A second problem associated with GHR projects is that most people suffering from the disease do not in fact have a family member with the disorder.<sup>56,61,62</sup> Any findings from GHR research cannot be readily generalized to the clinical population as a whole.

The aim of GHR research is to identify reliable and specific risk factors relevant to the disorders expression that are present in asymptomatic high-risk individuals. This would allow for a widespread schizophrenia screening program and, if necessary, the implementation of primary prevention strategies. Despite much effort, no such factors have been identified and primary prevention remains out of reach. As noted by Cornblatt and colleagues<sup>63</sup> and Mrazek and colleagues<sup>64</sup> the way forward now is that of indicated prevention. Although such prevention is an early form of secondary prevention, programs focusing on the schizophrenia prodrome signify a much more immediately possible strategy.<sup>64</sup> Such an approach allows for evaluation of putative risk factors identified by GHR research through development of prodromal criteria. For example, data from the New York High Risk Project<sup>65</sup> suggests impaired attention in premorbid phases may be causally associated with social deficits that emerge in later stages. As a consequence, the elucidation of prodromal risk factors remains crucial.

### **The Way Forward: Prodromal Markers**

From a developmental perspective, the premorbid stage of psychosis is followed by the prodromal stage, which in turn is followed by the onset of the psychotic stage. Therefore, markers evident in the prodromal stage develop at separate, later time points relative to premorbid indicators. It follows then, that a major advantage of identifying prodromal

markers is that they are significantly closer to illness onset, and therefore have markedly improved predictive power. A further advantage of studying vulnerability markers in this unique patient group is that whilst ensuring likelihood of becoming psychotic, iatrogenic effects and acute symptomatology which all too often plague chronic and first episode patient research, are removed. The utility of such markers would be in the identification of individuals that may benefit from early treatment. Since ARMS criteria rely on clinical risk, findings are more applicable to schizophrenic populations than traditional high risk research that rely on genetic risk alone. It is these factors, in addition to the palliative nature of neuroleptic treatments, that have resulted in the schizophrenia prodrome fast becoming the holy grail of schizophrenia research.<sup>27,63</sup> The features identified could be examined and their utility in predicting psychosis studied, with the ultimate aim of developing “warning signs” indicative of impending psychosis.<sup>63</sup>

### **Findings from Prodromal Marker Research**

Current prodromal research often incorporates the evaluation of putative risk factors.<sup>65</sup> Yung and McGorry<sup>66</sup> note that by establishing effective ARMS diagnostic criteria, the research focus can shift to the identification and validation of psychological and biological risk factors for psychosis.

Neuroimaging research with chronic and first episode patients has demonstrated that hippocampal volumes in this group of patients is markedly reduced.<sup>67</sup> Preliminary findings of Yung and colleagues<sup>68</sup> showed the ARMS group members had significantly larger hippocampi volumes than controls, and those who subsequently developed psychosis show significantly larger left hippocampi than those members who did not. Conversely, a later study<sup>63</sup> by the same research group found hippocampal volumes of ARMS patients at intake lie midway between those of normal controls and those diagnosed with schizophrenia, which is consistent with the neurodevelopmental theory of schizophrenia. This latter study found that larger left hippocampi volumes in ARMS group members was predictive of transition to psychosis.<sup>68</sup> Pantelis and colleagues<sup>31</sup> found that these members of the ARMS group who went on to develop psychosis exhibited reduced grey matter volumes in several areas of the brain, including the hippocampus and posterior hippocampal gyrus. These tentative findings are indicative of progressive changes in brain structure in areas such as hippocampal volume, which are accompanied by psychotic symptoms, are now the subject of fur-

ther research. Indeed, if proven, the prospect of early intervention preventing the development of these processes would be exciting. At present, no definitive risk marker has been identified from studies of brain structure and function.

Stress has long been associated with the development of schizophrenia.<sup>68</sup> The relationship between the possible role of stress, the hypothalamic-pituitary-adrenal (HPA) axis and the development of psychosis is currently being explored in the ARMS group.<sup>70</sup> Specifically, indicators of HPA function such as cortisol levels, self-reported stress and coping strategies and other interrelated factors are being investigated.

Other variables identified by GHR research as potential liability markers have been examined at the PACE clinic. Possible risk factors which have been investigated include obstetric complications, delayed childhood milestone attainment and childhood behavior. Early findings from ARMS work suggest that these risk factors do not predict impending psychosis, and it has been postulated that this is due to high levels of other Axis I disorders in members of the ARMS group who did not develop psychosis.<sup>71</sup> Increased maternal age (>30 years) was, however, found to be associated with risk of developing psychosis within a 12-month follow-up.<sup>71</sup>

Perhaps one of the most consistently investigated liability markers in schizophrenia research is that of neurocognition. For example, neuropsychological deficits have been reported among both stable and acutely psychotic schizophrenic patients in first-episode work and GHR studies and within other domains of the schizophrenia spectrum, such as schizotypal personality disorder. It is hoped that the detection of neurocognitive deficits in prodromal state patients may provide a liability marker for the development of future psychosis. Such findings would lend further support to the proposition that schizophrenia is a disorder of information processing. Findings by Brewer and colleagues<sup>72</sup> support the developmental view that ARMS individuals have neurocognitive abnormalities midway between normal controls and first episode psychosis patients. This has been replicated by Hambrecht and colleagues,<sup>73</sup> who also found that recent onset neuropsychological deficits were moderately predictive of psychosis development. In summary, it is extremely likely that neuropsychological deficits evident in the prodromal stages of schizophrenia constitute a biobehavioral liability marker.

Research into other potential markers evident in prodromal patients is flourishing, with groups look-

ing at factors such as sensory gating deficits identified by the prepulse inhibition and cytochrome P50 event-related potential paradigms, as well as deficits in olfactory recognition and the arachidonic acid lipid cascade as identified by the niacin skin flush test. Although such research is in its infancy, it is hoped that resultant findings may help to characterise the way forward for future research in this subject group.

### LIMITATIONS

The ethical implications of providing intervention therapy for a condition that only theoretically leads to an illness as serious as schizophrenia are sizable. Clinical trials evaluating the efficacy of antipsychotic medication in this group are currently ongoing,<sup>74</sup> however, even the existence of such studies remains contentious issue and is hotly debated. Antipsychotics, even atypicals, may have various detrimental effects when administered in this group. Several investigators have found the developing neocortex of young adults is particularly vulnerable to dopaminergic exposure.<sup>75,76</sup> Antipsychotic medication typically controls the positive symptoms of schizophrenia and exhibits little efficacy on negative symptoms. Attenuated negative symptoms have been found to predate attenuated positive symptoms, hence negative symptoms may reflect the underlying core vulnerability which needs to be addressed first, rather than the resultant positive symptoms.<sup>27,63</sup> In this way, pharmacological treatment would make the transition from controlling symptoms to affecting the underlying psychopathological processes. Additional problems associated with antipsychotic therapy include the high prevalence of side effects, such as excessive weight gain, lipid elevation, and diabetes. Furthermore, the stigmatization and unknown detrimental psychological effects may negate any positive effects of early intervention.

Research into alternative treatments to antipsychotic medications is now underway. The hope is that such interventions may offer the ability to prevent psychosis with favorable side-effect profiles. At present no such alternatives have been shown to work and although not without significant adverse effects the currently available atypical antipsychotic medications can often be administered in low enough doses to avoid serious tolerability problems. Cornblatt and colleagues<sup>27</sup> report that antidepressants in their CHR- group are as effective as antipsychotic therapy. Indeed, given the evidence suggesting neurocognitive deficits may be a causal component in the development of psychosis, treatments with cognitive enhancer drugs or cognitive-remediation therapy may be the most appropriate.

Even if liability indicators are established for this subgroup, there is no reason to suggest that identification of such markers will provide any clue to relevant treatment. It is highly likely that many risk factors that are identified will not be directly causally related to psychosis. Such factors need to be eliminated, since treatments aimed at such non-causal risk factors are spurious.<sup>77</sup> Bovet and Gamma<sup>78</sup> note that most prevention programs are performed by clinicians and, as such, relying on neuropsychological and psychophysiological data would be unwise.

## CONCLUSION

With the development of diagnostic tools identifying ARMS individuals, a flurry of research into possible prodromal markers of vulnerability has ensued. The identification of such markers would provide researchers with the ultimate tool: the robust identification of people at imminent risk of developing psychosis. Unfortunately, much like schizophrenia itself, there is likely to be a cluster of markers, rather than one predictive marker. However, if this matrix of risk factors can be collated meaningfully the implications for mental health would be huge. Such an achievement would have multiple financial, scientific and therapeutic gains.

The development of preventative interventions becomes increasingly feasible with the rapid accumulation of vulnerability markers to psychosis. They offer the tangible possibility of ultimately identifying individuals at risk from psychosis well before onset. The potential scientific and therapeutic returns from such a scheme would be considerable. **CNS**

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